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Title: Open Challenges in the Management of Autoimmune Hepatitis

Running Title: Open challenges in AIH

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Abstract

Autoimmune Hepatitis (AIH) is a rare autoimmune disease of the liver with many open questions as regards its aetiopathogenesis, natural history and clinical management. The classical picture of AIH is chronic hepatitis with fluctuating elevation of serum transaminases and Immunoglobulin G levels, the presence of circulating autoantibodies and typical histological features. However, atypical presentations do occur and are not well captured by current diagnostic scores, with important consequences in terms of missed diagnoses and delayed treatments.

AIH is treated with corticosteroids and immunosuppressive drugs but up to 40% of patients do not achieve full biochemical response and are at risk of progressing to cirrhosis and liver failure. Moreover, standard therapies are associated by significant side-effects which may impair the quality of life of patients living with AIH. However, advances in the understanding of the underlying immunology of AIH is raising the prospect of novel therapies and optimisation of existing therapeutic approaches to reduce side-effect burdens and potentially restore immunological tolerance.

In this review we outline the clinical characteristics, aetiopathogenesis and management of AIH and current challenges in the diagnosis and management of AIH and provide evidence underlying the evolution of diagnostic and clinical management protocols.

Introduction

Autoimmune Hepatitis (AIH) is a rare liver disease characterized by autoimmune inflammation of the liver with the potential for progression toward cirrhosis, liver failure and death . It was first recognized by Jan Waldenström in 1950 in a young female patient who was diagnosed with chronic liver disease and hypergammaglobulinaemia. Over the time, the discovery of AIH-associated autoantibodies further refined its specific clinical picture and in the '90s validated, diagnostic criteria were developed.

Current therapies include steroids and immunosuppressive agents that were not developed specifically for AIH. Their efficacy in reducing mortality was demonstrated from the 1970s in several small, single-center, randomized controlled trials and, despite multiple efforts by the scientific community, no specific, targeted treatments have been developed for AIH. Yet, over the last decade, the pathogenesis of AIH has been better elucidated and new promising agents have drawn attention.

In this review we will briefly present the epidemiology and clinical picture of AIH, discuss open issues in the clinical management of the disease and, based on the available evidence on its pathogenesis, introduce new therapeutic approaches under study.

Epidemiology

Autoimmune hepatitis occurs more frequently in women than men, by a ratio of 8:2. Female preponderance is typical of most autoimmune diseases and is likely driven by a combination of genetic, hormonal and environmental factors[1]. AIH has been observed in populations worldwide and can occur at all ages[2]. There is a bimodal distribution of the age of onset, with a small peak around adolescence and a second one around the age of 40-50[3].

A scarcity of population-based studies has limited accurate estimates of point prevalence; one of the more comprehensive studies published so far, a nationwide registry-based cohort study from Denmark, reported a prevalence of 23.9 (95% Confidence Interval 22.6 to 25.2) per 100,000 inhabitants in 2012. The incidence of AIH has been estimated to range from 1.5 cases per 100,000 individuals per year in Japan to 3.0 cases per 100,000 individuals per year in the United Kingdom[4]. The diffuse adoption in most healthcare services of the 10th version of International Classification of Disease, which contains a specific code for AIH, will likely benefit future epidemiological studies.

There has been a progressive increase in new cases of AIH over the last decades[3,5,6]. Although different ascertainment methods and changes in definition and diagnostic criteria may have played a role, this trend has been observed worldwide and a range of environmental factors have been implicated. Additionally, although AIH is less common in older patients there is evidence suggesting that the recent increase in the incidence of AIH may be driven by this group of individuals[6].

Pathogenesis part 1: the interaction between genetic background and environmental factors

AIH occurs as a result of the loss of immune tolerance to self-antigens with subsequent damage to the liver mediated by the immune system. As with most autoimmune disorders, there is an interplay between environmental factors and host susceptibility factors that results in the loss of self-tolerance.

Genetics

A genetic predisposition to AIH is supported by the observation of an increased prevalence of AIH within families, despite a very low risk and low concordance in monozygotic twins[7]. The only Genome-wide Association Study (GWAS) performed in AIH to date was carried out in a Northern European population and demonstrated the strongest genetic association with class II HLA (human leukocyte antigen), confirming suggestive findings from pre-GWAS era studies[8]. The HLA variants identified in this study are DRB1*03:01 as primary and DRB1*04:01 as secondary susceptibility genotypes. A range of other HLA-DR genotypes have been associated with increased AIH risk in other populations in targeted studies (reviewed in[9]). Interestingly, the distribution of HLA genotypes is different across ethnic groups, which may partly account for clinical differences in the disease course of AIH. As well as influencing the risk of disease, some HLA-DR genotypes appear to influence the age at presentation, natural history of disease, treatment response, auto-antibody profile and other laboratory abnormalities[10,11]. Overall, the importance of class II HLA in the risk of AIH, as with other autoimmune diseases, illustrates the central importance in antigen processing, presentation and activation of CD4 T helper cells in the pathogenesis of AIH.

Other putative genetic variants have been identified from both the GWAS study and targeted studies of pre-selected genes, which predictably have been focused on pathways that regulate immune responses. For example, variants that may reduce the activity of the regulatory molecule Cytotoxic T Lymphocyte Antigen 4 (CTLA-4), which functions to prevent T cell costimulation and activation, are over-represented in AIH[12,13]. SH2B3, a negative regulator of cytokine receptor signalling, was identified in the GWAS of AIH[8]. Variants in tumour necrosis factor α[14], the vitamin D receptor[15], transforming growth factor β[16] and the T cell death receptor Fas[17] have all also been reported.

The variants described above relate to the presentation of antigen to T cells and the regulation of T cell activity and are similarly seen in other autoimmune disorders. Coupled with the association of AIH with the presence of other autoimmune conditions and a family history of autoimmunity, this suggests that AIH may occur as a consequence of a generalised low threshold of T cell activation.

Environmental factors

It is presumed that in AIH an environmental factor triggers the loss of self-tolerance in a genetically susceptible individual. A range of putative triggers for AIH have been proposed, including drug exposure and viral infections, although no universal trigger has yet been identified.

Drug-induced AIH is well described[18], with an acute hepatitis and positive auto-antibodies being formed after exposure to drugs such as nitrofurantoin and minocycline. Metabolites of older medications responsible for drug-induced AIH, including tienilic acid and dihydralazine, have been shown to bind Cytochrome P450 enzymes in the liver, forming neoantigens that act as a target for immune responses[19,20]. Anti-TNFα drugs are also associated with a drug-induced AIH[21].

Infection with a range of pathogens has been implicated in the onset of AIH[22] with viral infections receiving the most attention. There is overlap between several viral antigens and AIH, most notably in cytochrome P450-2D6 which is the target of anti-LKM-1 autoantibody seen in type II AIH, and has high homology to Hepatitis C, Epstein-Barr, Herpes Simplex-I and cytomegalovirus antigens. Anti-LKM-1 seropositivity is recognised in HCV infected individuals and an association between HCV and AIH is described[4].

Histological features compatible with AIH have been observed following or coincident with infection by human herpes viruses, measles and hepatitis A, B and E viruses suggesting that viral infection may be an important trigger in at least some presentations of AIH (reviewed in[9,22,23]). Other infective triggers have been proposed including *Rickettsia*[24] and parasitic infections. Changes in the gut microbiota associated with systemic autoimmunity[25] may also be relevant to the pathogenesis of AIH.

Drugs, infective triggers, vitamin D deficiency[26] and other exposures yet to be described, are believed to lead to the loss of peripheral tolerance and generation of autoimmune responses by various mechanisms: the unmasking of previously tissue restricted antigens, the formation of neoantigens, cross

reactivity – whereby immune receptors recognise an exogenous antigen but also bind liver antigens – bystander activation of previously constrained auto-reactive T cells in inflamed tissue or impairment of immunoregulatory mechanisms[27]. Circulating auto-reactive T cells are present but constrained in healthy individuals[28,29] suggesting that in health the autoreactive immune cells required for autoimmunity are universally present but that mechanisms of peripheral tolerance hold this in check. The importance of this peripheral tolerance in liver immunity is demonstrated by the acute immune-mediated hepatitis which can occur following immune checkpoint blockade immunotherapy for cancer[30].

Pathogenesis part 2: Mechanisms of liver damage

Whatever the specific trigger and underlying genetic susceptibilities contributing to autoimmune activation, a cascade of downstream signals and effector mechanisms result in liver inflammation and damage (reviewed in detail in[4,23,31,32]). Central to the pathogenesis of AIH is the activation and recruitment of CD4 T cells to the liver[33] which occurs following recognition of self-antigens presented in the context of class II HLA by professional antigen presenting cells. Naïve CD4 T cells differentiate into Th1, Th2, TfH and Th17 lineages upon activation depending upon the local costimulatory and cytokine environments, and all these subtypes contribute to AIH.

Th1 CD4 T cells secrete INF-γ and IL2 which results in the recruitment and activation of innate effector cells including macrophages and adaptive cytotoxic CD8 T cells and increases expression of class I and class II HLA, increasing antigen presentation. Unusually, hepatocytes themselves can express both class I and II HLA and do so in AIH but not in health[34,35]. Perforin and granzyme B expression, both effector molecules of cytotoxic CD8 T cells, are upregulated in the liver of patients with AIH[36].

Th2 and TfH cells secrete other cytokines including IL4, IL10 and IL13 and provide B cell help resulting in B cell activation, proliferation and maturation into antibody secreting plasma cells. These result in complement activation, and direct hepatocyte damage[23].

Th17 CD4 T cells have increasingly been noted to be important in the pathogenesis of AIH[37,38]. They are pro-inflammatory cells and differentiate in the presence of IL6, and secrete IL17 which in turn

increases hepatocyte IL6 production, potentially enhancing further Th17 differentiation[39,40] and hence may have a pivotal role in the perpetuation of the autoimmune activity in AIH.

Coupled with increased inflammatory effector cell differentiation, there is impairment of cellular immunoregulation (reviewed in[41]). Treg are a subset of CD4 T cells which function to restrain conventional CD4 and CD8 T cell activity by a range of mechanisms. There is evidence for functional impairment and reduction in frequency of Treg from patients with AIH[42–45] although this has not been replicated in all studies and functional assessment of Treg from the liver of patients with AIH remains lacking. There is evidence that the inflamed liver microenvironment may further impair Treg function[46]. Differentiation of Treg is also impaired in the presence of IL6, resulting in Th17 differentiation, shifting the balance further towards inflammation than tolerance[39]. More recently a subset of B cells with regulatory activity (Breg) have been implicated in several autoimmune disorders[47] and it remains to be seen whether they play a role in AIH.

Pathological findings

Histology

Histological assessment is central to the accurate diagnosis of AIH[48] and is a pre-requisite to apply the International Autoimmune Hepatitis Group simplified scoring system[49] and to make a definite diagnosis of AIH[50].

Histology in AIH serves several roles:

- Accurate diagnosis of AIH and exclusion of alternative diagnoses
- Identification of concomitant liver pathology (e.g. steatohepatitis)
- Assessment of disease activity (e.g. prior to treatment withdrawal)
- Assessment of disease stage (i.e. the presence of fibrosis or cirrhosis at presentation)

The histological features observed have been grouped as typical or compatible for AIH (**Table 1**) and are discussed in detail in[51].

The historical cardinal features of classic AIH are the presence of interface hepatitis, the presence of a predominantly lymphoplasmacytic infiltrate, emperipolesis and hepatocyte rosetting.

Interface hepatitis is a typical feature of AIH, characterised by a portal inflammatory infiltrate which crosses the limiting plate, extending into the lobule, and may be associated with hepatocyte necrosis. The infiltrate is predominantly lymphocytic and often plasma-cell rich but also composed of histocytes, eosinophils and neutrophils. However, plasma cells are not observed in a substantial minority of patients[51] and interface hepatitis is not a universally observed feature[52].

Hepatic rosettes are rings of hepatocytes arranged around a central lumen, and represent a regenerative process within the liver. Rosettes are a typical feature of AIH histology[49,50] and are observed in 49% of biopsies from patents with active disease, although again are not specific to AIH[52].

Emperipolesis, the presence of a lymphocyte or plasma cell within the cytoplasm of a hepatocyte, is observed in up to 65-78% of liver biopsies and is associated with disease activity and hepatic fibrosis[52,53]. This process derives from a native mechanism of hepatic immunotolerance[54].

None of these features is pathognomonic of AIH alone and may be present in other conditions such viral hepatitis, Wilson's disease or Drug-Induced Liver Injury (DILI)[4]; nevertheless, the presence of severe interface hepatitis and a rich plasmacellular infiltrate in a patient with high pre-test probability (for example high titre Anti-Smooth Muscler Antibodies (anti-SMA) positivity and high serum IgG levels) strongly support the diagnosis of AIH. The lack of sensitivity and specificity of rosettes and emperipolesis, whose presence is required by simplified diagnostic criteria to receive the highest score as regards histological items, calls for their revision in the future[55]. A novel histological score has been proposed in 2017 by Balitzer and colleagues[55]. This new scoring system was found more accurate than in the features in the simplified criteria avoids dependence on hepatocyte rosettes and emperipolesis which are not universally observed in AIH.

In cases of Acute Severe AIH (AS-AIH) with acute liver failure (ALF) different histological features should be expected; the centrilobular zone is the most affected region of the parenchyma, and central

perivenulitis, plasmacellular infiltrate, diffuse hepatic necrosis with scavenger macrophages, lobular hepatitis, and lymphoid follicles are observed[56].

Although there are no uniquely diagnostic features pathognomonic of AIH, it is typically straightforward to exclude other immune-mediated liver disorders such as primary biliary cholangitis and primary sclerosing cholangitis. However, the similarity of features of AIH with DILI and some viral infections can lead to diagnostic uncertainty. Compared to DILI, typical AIH is suggested by severe portal inflammation rich in plasma cells, lack of cholestatic features and some degree of fibrosis[51]. Yet, DILI with immune features might be eventually indistinguishable even after liver biopsy and in some cases only a subsequent relapse after stopping immunosuppression may clarify the clinical picture.

Moreover, the rising rising incidence of Non-Alcoholic Fatty Liver Disease (NAFLD)/ Non-Alcoholic Steatohepatitis (NASH) worldwide should be considered carefully, and nearly 20-30% of patients with AIH have histological signs of NAFLD/NASH in the US[48]. Since around 19% of patients with biopsy-proven NASH are antinuclear antibodies (ANA) positive[57], in a patient with a high pre-test likelihood for NASH a significant periportal inflammation dominated by lymphocytes and plasma cells is required to make a concomitant diagnosis of AIH.

Serological abnormalities

AIH has characteristic serological abnormalities with elevated serum IgG concentrations observed in 85% of patients at diagnosis[2], alongside specific circulating auto-reactive antibodies (summarised in **Table 2**). Hallmark antibodies are ANA, anti-SMA and anti-Liver Kidney Microsomal antibody-1 (anti-LKM-1): the latter two are important for distinguishing between type 1 and type 2 AIH, respectively[58]. These major diagnostic antibodies are detected by indirect immunofluorescence on rodent gut, liver and renal sections although other auto-antibodies (**Table 2**) may be detected by enzyme linked immunosorbent assays (ELISA) or immunoblot techniques[59]. Around half of AIH patients with detectable autoantibodies have only one of these three autoantibodies, while the other half have two or more present[48].

ANA are observed in 34-80% of patients with AIH[60,61] and were the first autoantibody associated with AIH[62]. The presence of ANA alone has low sensitivity and specificity for AIH (65% and 75% respectively)[63]. ANA positivity is observed in other conditions including systemic lupus erythematosus, and other differential diagnoses for AIH, including DILI and NAFLD, making differentiation between these on serological grounds challenging. A significant ANA titre in adults is ≥1:40 and ≥1:20 in children, and staining is typically homogenous although speckled patterns are also observed[2].

Anti-SMA are observed in type I AIH in 53-63% of patients[60,61]. Similarly to ANA, anti-SMA is neither completely sensitive nor specific for AIH (59% and 93%, respectively)[63], although combined presence of both ANA and anti-SMA improves both sensitivity and specificity[60]. Anti-SMA antibodies bind antigens that compose the cytoskeleton of smooth muscle, the most specific sub-type being anti-F-actin, however ELISA testing for F-actin alone reduces sensitivity compared to immunofluorescence as actin is not the sole target antigen for anti-SMA in AIH.

The presence of anti-LKM-1 is the hallmark of type 2 AIH, seen in two thirds of these patients but absent in type 1 AIH[61], and stains the cytoplasm of hepatocytes and the pars recta of the proximal convoluted renal tubule. The target antigen has been identified as the cytochrome P450 2D6 enzyme, and anti-LKM-1 positivity is recognised in hepatitis C[64], amongst other liver diseases, so is again not specific for AIH. A significant titre is accepted to be ≥1:40 in adults and ≥1:10 in children[58].

Nearly 20% of subjects with AIH are seronegative for ANA, SMA and LKM1 and testing for an extended panel of auto-antibodies should be considered (**Table 2**) [48].

Clinical features

The clinical onset of AIH is heterogenous, and spans from asymptomatic onset to fulminant acute liver failure[2]. The most frequent clinical picture at presentation, seen in nearly two thirds of patients[2], includes non-specific symptoms such as fatigue, malaise, anorexia, weight loss, polyarthralgia without arthritis, associated with abnormalities in liver enzymes, typically in the form of chronic hepatitis. One of the features associated with AIH is the fluctuation of transaminases over months, associated with episodes of increase in Aspartate transaminase (AST)/ Alanine transaminase (ALT) up to three/five times the upper limit of normal. One third of patients present with established cirrhosis, which is likely driven by long standing subclinical inflammation, and the early diagnosis of AIH represents an ongoing challenge, as cirrhosis is associated with poorer long-term prognosis[65]. Guidelines suggest that around 25% of patients present with acute hepatitis[2], although some series reports up to 70% [66].

The definition of acute AIH remains non-standardized. A pragmatic and readily applicable categorization is outlined here[66]:

Acute AIH – when hepatitis with jaundice are present

Acute Severe AIH (AS-AIH) – when coagulopathy (INR ≥ 1.5) is present

AS-AIH with Acute Liver Failure (ALF) – when hepatic encephalopathy is also present

These definitions have been incorporated in the most recent American guidelines[48]. Despite lacking supportive evidence, they readily identify three distinct scenarios well recognized by clinicians, which should prompt different therapeutic approaches, in particular consideration of listing for liver transplantation. AS-AIH with ALF and AS-AIH are often challenging to recognize as many patients may not have the specific classical serological features of AIH: IgG levels are frequently within the normal range[67], autoantibodies may be negative[68] and histological features are different from classical chronic active hepatitis. Therefore, underdiagnosis may occur with current diagnostic criteria[69] and there are discussions to update the diagnostic criteria to take into account the complexity of different presentations of AIH.

Paediatric AIH has differing presenting features to adult: more than 50% of children present with established cirrhosis at diagnosis and a more aggressive disease course compared to adults is observed.

Type 2 AIH is characterized by pediatric onset, it is rarely diagnosed in adulthood and it is associated with frequent relapses[70]. Autoimmune sclerosing cholangitis is a variant syndrome present only in children which is as frequent as classical AIH in this age group (see Variant Syndromes).

Diagnosis

Current diagnostic criteria for AIH are limited in their accuracy due to the heterogenous nature of the disorder and frequent atypical presentations, therefore a high index of clinical suspicion is needed [48].

Diagnosis is dependent upon the combination of clinical features, laboratory and histological findings[49,50]. Radiology is helpful to exclude other processes such as cholangiopathy and for determining radiological stigmata of chronic liver disease, portal hypertension and exclusion of hepatocellular carcinoma, however AIH itself does not have specific radiological features. While the revised diagnostic score for AIH is predominantly a research tool, the simplified diagnostic criteria, developed in 2008, provides a rapid and reliable diagnostic tool[49]. These criteria are comprised of the exclusion of viral hepatitis, the presence of autoantibodies, serum IgG levels and the histological findings, allowing determination of a "Probable" or "Definite" diagnosis of AIH. The simplified diagnostic score is less sensitive than the revised diagnostic score (95% vs 100%, respectively).

It is well recognized that patients with seronegative AIH, AIH with normal IgG at diagnosis and AS-AIH do not fit the classical picture of AIH and their diagnosis may be missed by current diagnostic tools.

In patients without the classical circulating auto-antibodies, ANA, anti-SMA, anti-LKM1, extended screening for auto-antibodies screens should be undertaken (**Table 2**), and even if these are negative a seronegative AIH is a possibility. Seronegative AIH is most typically seen in acute AIH, which is associated with normal IgG levels and atypical histological patterns, or in patients with unexplained, cryptogenic chronic hepatitis. Prevalence of these subtypes are difficult to estimate, with wide ranges (around 7% for acute cases, 1-34% for chronic cases)[71].

AIH with serum IgG levels within the normal range has been poorly characterized until recently. 10% of all AIH cases have normal IgG levels at diagnosis[72] and are indistinguishable from patients with typical AIH, having similar biochemical and histological parameters and rates of treatment response. However, low gamma-globulins at diagnosis predict a higher chance of treatment withdrawal without relapse[73] and remission without treatment (seen in 24% compared to 8% in typical AIH cases[72]), suggesting a more favorable long-term disease course.

Variant syndromes

The presence of non-obstructive cholestasis in a patient with known AIH should raise suspicion of the possible concomitant presence of Primary Biliary Cholangitis (PBC) or Primary Sclerosing Cholangitis (PSC). Whilst during acute-severe forms of AIH it is not unusual to find some degree of cholestasis, the presence of progressive and/or persistent chronic cholestasis is not a feature of pure AIH.

Variant syndromes are rare and diagnostic criteria are not universally agreed[2]. The onset of features of AIH with PBC or PSC may be simultaneous or sequential and it remains uncertain whether these syndromes represent the co-incident presentation of two diseases, distinct pathological entities or points on a spectrum of pathology between AIH and the cholestatic liver diseases[74].

AIH-Primary Biliary Cholangitis

AIH with features of PBC has been reported in approximately 1 in 10 patients with AIH or with PBC, although this is variable depending upon the diagnostic criteria applied[2]. The "Paris criteria" have been proposed as tool to diagnose PBC in presence of AIH and have good sensitivity and specificity (92% and 97%, respectively) for clinically determined overlap[75]. They define AIH-PBC overlap as the presence of 2 of 3 major diagnostic criteria for both AIH and for PBC (**Table 3**). In addition, an absolute requirement for the presence of interface hepatitis is suggested to make the diagnosis. Isolated AMA positivity may occur in AIH without biochemical cholestasis or bile duct lesions on histology and do not necessarily evolve to overt PBC[76]. There remains a lack of consensus for the exact criteria for AIH-PBC overlap, and consideration of extended screening for auto-antibodies and close observation of treatment responses is appropriate.

Management of AIH-PBC overlap can broadly be considered to be a combination of the treatment approaches to both AIH and PBC independently (i.e. immunosuppression and ursodeoxycholic acid (UDCA)). However, as some patients respond fully to UDCA alone, and elevated transaminases and a lymphocytic inflammatory infiltrate are observed in PBC, it has been suggested that initial treatment with UDCA should be offered if PBC is felt to be the dominant pathological process with subsequent immunosuppression with corticosteroids if an insufficient biochemical response is observed[74]. A recent meta-analysis of treatment response comparing UDCA alone with UDCA combined with

immunosuppression showed no significant benefit for symptom control, biochemical improvement and non-progression of fibrosis with immunosuppression, although a benefit in transplant free survival was noted in studies with longer term follow up[77]. However, in those with marked interface hepatitis immunosuppression should not be delayed[78].

AIH-Primary Sclerosing Cholangitis

The diagnosis of AIH-PSC overlap is less standardized than AIH-PBC and lacks specific criteria, but requires the presence of histological or cholangiographic features of PSC with AIH. A confounding complication is the presence of a biliary pattern of histological injury observed in a minority of patients with AIH[51]. The application of the revised International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria for AIH to cohorts of PSC patients suggest that 9-14% of PSC patients meet accepted AIH diagnostic criteria[74].

Specific management recommendations for AIH-PSC are lacking due to an absence of trial data on this rare group of patients. The manifestations and monitoring of PSC are typically managed conventionally and immunosuppression offered with corticosteroids, azathioprine and other agents. Biochemical improvement in transaminases is observed with treatement[79] and the risk of hepatobiliary malignancy is lower in PSC-AIH compared to classical PSC, although overall risk of progression of liver disease is similar[80]. Adverse outcomes in AIH-PSC may be more frequent than in AIH alone or AIH-PBC[81].

Autoimmune Sclerosing Cholangitis

In children, the overlap between AIH and sclerosing cholangitis is found with similar frequency to AIH alone and is termed Autoimmune Sclerosing Cholangitis (ASC)[82]. Patients with ASC typically have circulating ANA and anti-SMA, high levels of IgG and the presence of interface hepatitis. ASC is associated with a worse prognosis that AIH and co-exists with inflammatory bowel disease in 45% of patients, compared to 20% of those with AIH alone[82].

All children with AIH should undergo magnetic resonance cholangiography at diagnosis[2] due to the frequency of ASC and the fact that biochemical evidence of cholestasis is frequently absent (i.e. the alkaline phosphatase (ALP) and γ-glutamyltransferase (γ-GT) may be normal) and there may be no

biliary injury evident on histology[4,82]. Whether this approach should be extended also to adults is still matter of debate as, for example, in a single center cohort, PSC was observed in up to 10% of newly diagnosed adults with AIH. Yet, differentiation between sclerosing cholangitis and biliary distortion due to advanced parenchymal fibrosis is challenging[83]. It is presumed not to be cost-effective to undertake Magnetic resonance cholangiopancreatography (MRCP) in all new adult presentations of AIH in absence of cholestasis or other clinical indications, but again, a high index of suspicion should be maintained.

The natural history of ASC is characterized by poorer response to treatment and more frequent progression to cirrhosis and liver failure than AIH alone and after reaching adulthood patients often shift toward a more "biliary" phenotype, with predominance of the sclerosing component over the hepatitic one[84].

Treatment guidelines for ASC suggest management with immunosuppression as for AIH and consideration of UDCA, although there are no prospective randomised controlled data available[4].

Management

The intent of pharmacological therapy in AIH is to reduce symptoms and liver inflammation, normalise liver function, prevent the progression of fibrosis and the evolution of cirrhosis and end stage liver disease.

Markers for treatment response in chronic AIH are:

- Reduction in serum transaminases
- Reduction in serum IgG levels
- Improvement in histological appearances
- Non-progression or improvement in non-invasive markers of fibrosis

The aim of treatment in practice is complete biochemical response, defined as the sustained normalization of both serum transaminases and circulating IgG[2,48]. This has been shown to be associated with lower rates of relapse, improvement in histological inflammatory activity and fibrosis and improved transplant free survival[65,85–87]. However, significant histological activity may be observed in patients with normal transaminases[88,89] which may be associated with adverse outcomes[90] . Therefore, although complete biochemical response is the principle target of treatment, non-invasive and invasive evaluation of disease progression should be tailored to the individual.

Induction phase

Corticosteroid therapy is the mainstay of therapy for the induction of remission in AIH and was shown to reduce mortality in studies dating back to the 1970s[91]. Prednis(ol)one is commonly used and recommended in current international guidelines at 0.5-1 mg/kg/day[2] or 40-60 mg/day[48] either as monotherapy or in combination with azathioprine. Corticosteroid doses are then weaned once clinical response is established. The exact dose of steroids may not have a significant impact on the likelihood of induction of remission[92].

Azathioprine (AZA) is introduced early during induction, either at the start of treatment or delayed for two weeks after starting corticosteroids and once jaundice has resolved. Delayed introduction allows confidence that response to steroids is established, appropriate pre-treatment screening and to ensure that AZA hepatotoxicity can be readily distinguished from non-response to corticosteroids. AZA in combination with corticosteroids has been shown to have similar efficacy to prednisolone monotherapy but with a lower side effect burden for patients[93]. Dosing is typically 1-2 mg/kg/day and screening for thiopurine methylytransferase activity (TPMT) prior to identify those with near absent activity who are at higher risk for myelosuppression with AZA should be considered[2,48]. AZA monotherapy for induction is not appropriate and is associated with higher mortality[94].

In practice, clinicians have highly variable prescribing preferences with regard to timing, dosing and weaning of corticosteroids and AZA[95]. Treatment approaches should be personalised and consideration given to the risks of medication side effects[2]. Induction of remission with corticosteroid monotherapy is an appropriate choice when AZA is contraindicated or not-tolerated. A suggested strategy for the management of AIH is shown in **Figure 1**.

There is a role for budesonide, as an alternative to predni**s**(ol)one, in the induction of remission. It was shown to be superior in the induction of remission with the absence of steroid specific side effects compared to prednisolone for patients with active (but not severe) AIH[96]. However, similar biochemical efficacy between budesonide and prednisolone is not definitively established and there are no long-term survival or histological response data available. Furthermore, budesonide is contraindicated in cirrhotic patients due to the risk of porto-systemic shunting bypassing its 1st pass hepatic metabolism. However, budesonide may be a good option in non-cirrhotic patients with moderately active AIH who are at significant risk for corticosteroid side effects[2,48], but it is not yet frequently prescribed in adult or paediatric settings[95].

Whilst efficacious regimens for the induction of remission in AIH exist, many open questions remain regarding induction of remission in AIH:

- What is the optimum starting dose of corticosteroids?
- Do prednis(ol)one and budesonide have equal efficacy?

- What is the optimum timing for the addition of AZA?
- Should steroids be trialled in acute liver failure secondary to AIH and what are the criteria for failure of response?
- Are alternatives to AZA, such as mycophenolate, thioguanine, ciclosporin, calcineurin inhibitors efficacious?
- Are there biomarkers which can predict or stratify treatment responses?
- What are the optimum treatment response markers (transaminases, IgG, histology, other biomarkers) and how do they correlate with long term outcomes?
- In the future will steroid free induction regimens be possible?
- How should failure of response be defined?

Maintenance of remission

Similarly to the induction of remission, drug therapy for the maintenance of remission is based upon AZA and corticosteroids. Following the induction of remission, corticosteroids are weaned to the lowest possible dose that maintains biochemical remission, with up-titration of AZA to 2mg/kg/day[2,48]. Corticosteroid-free maintenance with AZA monotherapy is the goal of treatment where possible[2], although a significant proportion of patients remain treated with corticosteroids[97]. Although AZA is superior to corticosteroid monotherapy for the maintenance of remission[94], in those with readily controlled disease who are intolerant of or are unwilling to take AZA, low dose prednisolone monotherapy (<10mg/day) is acceptable. The requirement for prednisolone (or equivalent) of ≥10mg/day may be considered a marker of insufficient response[98]. Despite the efficacy and generally good tolerability of AZA, approximately 15% of patients discontinue AZA by 1 year of treatment[99], predominantly due to intolerance.

Although therapeutic drug monitoring for AZA does not have prospective data to support its use, there is growing interest and the IAIHG have recently recommended its use[100] alongside international guidelines[2,48]. The principle advantages of therapeutic drug monitoring of AZA include:

- Dose optimization: retrospective data suggests that low thioguanine nucleotide levels are associated with higher relapse rates in adults[101]. Exact target ranges for thioguanine nucleotides remain undetermined as biochemical remission may be achieved at levels well below those required in inflammatory bowel disease[102].
- Assessment of treatment concordance: thioguanine nucleotide estimation also provides an objective measure of compliance with treatment.
- Identification of individuals who may benefit allopurinol-AZA therapy: AZA is metabolised via several pathways producing a range of metabolites. A significant proportion of patients produce an excess of 6-methylmercaptopurine (6-MMP). Excess 6-MMP is associated with toxicity and low-dose AZA with allopurinol may restore the balance of 6-thioguanine nucleotides and 6-MMP and improve clinical control[103].

Prospective data regarding the optimum target thioguanine nucleotide levels and the role for allopurinol-AZA therapy will be important in gaining optimal use of AZA in AIH.

Patients with insufficient response, requirement of significant doses of prednisolone (≥10mg/day) or intolerance to AZA or corticosteroids may be considered for second line therapies. Optimization and monitoring of therapy are important before determining failure of 1st line treatment as, to date, there are no prospective, randomised controlled trials to support other therapeutic combinations. Reconfirmation of the diagnosis, exclusion of concomitant alternative liver diseases (for example NAFLD) and consideration of treatment concordance, dose optimization of AZA with therapeutic drug monitoring, combination allopurinol-AZA therapy and the use of budesonide if corticosteroid side effects are encountered, should be undertaken.

Second/third line treatment

Treatment of AIH with AZA and/or corticosteroids is well established, however approximately 20% of patients have an insufficient response to this approach due to inadequate response or treatment intolerance[104]. These patients require a change of treatment to second and then third line agents.

Intolerance of AZA may be managed by conversion to alternative thiopurines. Switching to mercaptopurine resulted in 15 out of 20 patients achieving some degree of biochemical response in a retrospective case series of AZA intolerant patients, although it is unlikely to be useful in those with insufficient response to AZA[105]. There is growing interest in the use of t(h)ioguanine and a retrospective case series of 52 patients has reported efficacy and tolerability in patients with either intolerance or inadequate response to AZA[106].

If there is insufficient response to or intolerance of thiopurines, mycophenolate mofetil (MMF) is usually offered as a second-line treatment. Whilst there are currently no published, prospective randomised controlled trial data supporting the use of MMF as a second-line agent in AIH, multiple retrospective cohort studies and two recent meta-analyses have demonstrated biochemical response in 58%-78% of patients, and evidence for histological remission[107,108]. Those treated with MMF due to AZA intolerance had higher biochemical response rates (82%) than those with insufficient response to AZA (32%)[107]. Response rates to MMF in paediatric patients appear lower than in adults, but it remains efficacious and better tolerated than alternatives such as ciclosporin[109]. Whilst an effective and well tolerated medication, MMF is inappropriate for both men and women who are attempting to conceive and during pregnancy and alternatives should be considered.

Failure of these therapies should once again prompt revisiting the diagnosis and compliance with medication before adding/switching to other agents. Third line treatments used in AIH are:

- Calcineurin inhibitors - tacrolimus and ciclosporin
- Rituximab
- Infliximab.

There are also case reports and small case series reporting the use of cyclophosphamide, mTOR inhibitors and methotrexate[100]. None of these agents has been subject to randomised controlled trialling and the majority of evidence has been extrapolated from post-transplant immunosuppression and retrospective cohort studies.

Tacrolimus is most frequently used as a third line agent, more so in transplant centres[95]. Complete biochemical response rates to tacrolimus are similar to MMF when used as a second-line agent and in

those with intolerance based on recent meta-analysis[110]. Ciclosporin is often favoured in paediatric settings.

Rituximab use in AIH has been shown to be efficacious with significant improvement in liver enzymes, normalization of serum IgG and reduction in corticosteroid requirements with minimal infective complications in adults and potentially children[111–113]. However, the published experience equates to 30 rituximab treated patients, the majority in a single retrospective study.

Infliximab has been proposed as a third line treatment for AIH and efficacy has been reported in small numbers of adults and children[114–117]. There are concerns regarding chronic infections (especially *Mycobacterial* infection) and hepatotoxicity, but these need to be weighed against the risks of inadequately treated AIH and the potential toxicity of other treatments.

The recent position statement from the IAIHG and European Reference Network on Rare Hepatological Diseases does not make recommendation on the specific choice of agent that should be offered as a third line agent, nor whether they should be offered in combination with standard mediations or given alone[100]. It is worth discussion with expert centres and the Clinical Patient Management System, hosted by the European Reference Network on Rare Hepatological Diseases, provides the opportunity for an international expert panel to review the case[100]. Medication choice should be tailored to patient characteristics, patient and clinician preferences and availability. Consideration should be given as to whether a patient is eligible and interested in clinical trials of novel agents.

Side effects and optimizing therapy

Available therapies for AIH carry several side effects that should be thoroughly discussed with patients to reduce non-adherence rates. Side effects of steroids are well described and include both cosmetic and systemic changes. Chronic use of steroids is associated with osteoporosis, type 2 diabetes, hypertension, hyperlipidemia and increased risk of infections[118].

AZA is associated in the short-term with gastrointestinal complaints, but more significantly with pancreatitis, bone marrow suppression and acute hepatitis, alongside a risk of non-melanomatous skin cancer and potentially lymphoma. AZA is discontinued in approximately 14% of those treated, often due to intolerance[99]. Screening for TPMT activity prior to treatment does not allow identification of

those who will experience common side effects such as nausea, vomiting, hepatotoxicity or dose-dependent pancytopenia but does allow identification of those at risk of severe myelosuppression[48]. MMF shows a similar profile of toxicity to AZA (although with diarrhoea more commonly than nausea/vomiting) but is also teratogenic. Calcineurin inhibitors (tacrolimus and cyclosporine) are associated with neurological side effects, renal toxicity, hypertension, type 2 diabetes and hair loss.

There is a significant impact of both current treatments and disease activity upon patients' quality of life. Mood disturbance, depression, anxiety, cognitive dysfunction, chronic fatigue and decreased physical activity are all observed[119–121]. Corticosteroid use is significantly associated with adverse measures of quality of life, even after controlling for biochemical disease activity[121]. Clinicians and patients must be aware of the detrimental impact of treatment on quality of life which should be pro-actively monitored by clinicians.

Bone protection

Osteoporosis is observed in 16% of patients with AIH, while osteopenia is found in 43%[122]. The risk factors for low bone mineral density are similar to those for the general population including older age, low body mass index (< 23 kg/m^2), prolonged use of steroids (> 90 months) and also the presence of advanced fibrosis[122]. Even treatment with low-dose prednisolone (< 5.0 mg/day) or budesonide is associated with increased risk of fractures[123].

AIH patients should be screened at baseline and every 2 to 3 years with dual-energy X-ray absorptiometry. Elemental calcium (1 to 1.2 grams per day) and vitamin D (at least 800 International Units (IU) per day) should be given during treatment with corticosteroids and if vitamin D is insufficient. Bisphosphonate treatment should be prescribed according to international and local guidelines, based on risk score proofing such as FRAX® tool (https://www.sheffield.ac.uk/FRAX/tool.aspx). A recent single-center observational study reported good outcomes in terms of safety and efficacy of Denosumab treatment in patients with AIH[124].

Vaccinations

Ideally, vaccination status should be assessed before induction therapy. Patients with AIH should be vaccinated for Hepatitis A and B like all other patients with chronic liver diseases. Live, attenuated vaccines should not be given to AIH subjects on high doses of immunosuppression[2,48]. For most other vaccines there are no specific guidelines for AIH, but it is advisable to vaccinate the majority of patients for Influenza and Pneumococcus, based on guidelines from systemic rheumatic diseases[125].

As of November 2020, the world is still fighting against the pandemic of COVID-19; there is limited evidence on the risk in AIH patients[126,127]. Should an inactivated vaccine become available for COVID-19 it would appropriate for AIH patients to be vaccinated against this.

Treatment withdrawal

AIH is a chronic condition that requires life-long maintenance immunosuppressive treatment in the majority of patients. However, withdrawal of treatment is a realistic possibility in a selected group of patients. Complete biochemical remission for at least two years is suggested prior to stopping treatment according to European and American guidelines[2,48] and up to 54% of patients stopping treatment may maintain remission over 2 years[128]. However, other studies have demonstrated relapse rates of 90% [129], however in this study IgG levels were not reported for half of the patients and whether the higher rates of relapse observed were associated with active disease that could have been identified by elevated IgG is unclear.

Consideration also needs to be given to the impact of a flare of AIH of treatment; caution should be exercised in those with advanced fibrosis/cirrhosis, those with life threatening onset or hard to treat disease, and those where high dose steroids to re-induce remission would cause significant harm (for example psychiatric co-morbidity, established mineral bone disease, poorly controlled diabetes or hypertension).

However, currently available tools to risk stratify patients for treatment withdrawal are inaccurate. Up to 45% of patients in biochemical remission have persistent inflammation at follow-up liver biopsy, which is associated with higher frequency of relapse and worse transplant-free survival[90], suggesting that biochemical remission may not be an accurate representation of quiescence. Biochemical parameters lower than conventional laboratory upper limits of normal may predict patients that have a

lower chance of relapse, with ALT levels less than half the upper limit of normal (ULN) and IgG levels less than 12 g/L associated with better chance of relapse-free treatment withdrawal[128].

Based on the limitations of biochemical markers to predict treatment free maintenance of remission, pre-withdrawal liver biopsy should be considered: European Association for the Study of the Liver (EASL) guidelines suggest a liver biopsy for patients with severe initial presentation and for those patients at higher risk of harms deriving from induction therapy[2]; American Association for the Study of Liver Diseases (AASLD) guidelines encourage liver biopsy prior to treatment withdrawal to identify ongoing inflammation[48]. Although the rationale for a pre-treatment withdrawal liver biopsy is to identify ongoing inflammation not reflected in biochemical tests, an absence of histological activity coupled with biochemical remission, is not a guarantee of successful treatment withdrawal. In a study of treatment withdrawal in 30 patients, 5 out of 11 patients (46%) with no evidence of significant inflammation on liver biopsy and complete biochemical remission relapsed[128]

Therefore approaches to treatment withdrawal in AIH are unsatisfactory and not standardized; in the absence of more robust evidence to guide clinical management, clinicians and patients need to make individualised decisions based upon the potential benefits of stopping therapy, the natural history of that patient's disease and response to treatment, the potential for harm from progressive disease or disease flares, the risks of reinstitution of therapy, whilst accepting a significant likelihood of relapse over time.

Liver transplantation

There are three principle roles for liver transplantation in AIH: the treatment of chronic liver failure, the management of hepatocellular carcinoma in cirrhotic patients with AIH and the management of AS-AIH with ALF. Liver transplantation for all three indications is offered as per the criteria for transplantation in chronic liver disease, hepatocellular carcinoma (HCC) and acute liver failure of other causes. The outcomes following transplantation are broadly similar to other indications (5 and 10 year patient survival 79.4% and 70.8% respectively), although early complications from infectious diseases are more common than for other indications[135] . AIH recurs in the grafted liver following transplantation in 22% of patients[131].

Non-invasive assessment

The need for accurate and cost-effective methods to routinely assess liver fibrosis without invasive liver biopsy is well established. Whilst a liver biopsy is essential for the diagnosis of AIH, its use to monitor the progression of the disease over time has largely faded in favour of biochemical assessments. Yet, liver biochemistry may inaccurately reflect residual liver inflammation [90].

Non-invasive assessment of liver stiffness may have a role in AIH; patients achieving biochemical remission show a significant decrease in liver stiffness at transient elastography compared to those not achieving it[87]. Therefore, liver stiffness measurements may help avoiding unnecessary biopsies and strategies to target liver biopsies in, for example, those with a progressive increase of liver stiffness to titrate treatment may be possible, although evidence for this is awaited. A similar role for liver stiffness measurements may reduce the need for biopsies before treatment withdrawal. However, no data are available and longitudinal prospective trials are needed.

Risk stratification

Whilst risk stratification in AIH is challenging due to heterogeneity and rarity of the condition and the lack of validated risk stratification scores[132], there are several validated prognostic factors (reviewed in [70]). At presentation, the presence of cirrhosis[65] and antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP) positivity[133] have been associated with incomplete biochemical response and lower transplant-free survival rates. Younger age and higher IgG levels at onset, and type 2 AIH are all associated with higher rates of incomplete biochemical response[70]. During maintenance therapy, persistent elevation of transaminases and IgG[65,87] and persistent histological activity on liver biopsy[90] are associated with worse transplant-free survival.

Ethnicity has been associated with poorer prognosis in AIH. In Europe and the United States black ethnicity has been associated with difficult-to-treat AIH, younger onset, cirrhosis at presentation and reduced transplant free survival[13448]. Asian Americans and Hispanic Americans with AIH also experience worse outcomes compared to white Americans[48].

HCC occurs in patients with AIH and cirrhosis with an annual incidence of 1.1-1.9%[48]. Risk factors for HCC include persistent inflammation, use of immunosuppressive therapy for more than 3 years, presence of cirrhosis for more than 10 years and portal hypertension[48]. Therefore, all patients with advanced fibrosis /cirrhosis should undergo screening for HCC.

Unmet needs

Despite having some of the earliest controlled trials of therapy in the field of hepatology, there are many unanswered questions with respect to aetiopathogenesis, prognostication and management of AIH. Significant unmet needs persist for patients with AIH [132], which have been summarized in **Figure 2**.

Diagnostics

Although validated diagnostic criteria are established there remain many unanswered questions and challenges. For example, one third of patients have cirrhosis at diagnosis, which is associated with worse transplant free survival[65,135]. Whether this represents a group which have rapidly progressive fibrosis prior to diagnosis, or an indolent, protracted pre-symptomatic phase is unclear. It is important to identify these patients prior to the development of cirrhosis and, whilst population screening for AIH is unlikely to be cost effective, careful follow up of abnormal liver tests in primary care has the potential to improve liver disease detection rates[136].

Whilst histological assessment is essential for the diagnosis of AIH[49], the histological abnormalities observed are non-specific and hence diagnosis in the absence of classical changes and supportive serology remains challenging, leading to uncertainty for patients and clinicians and unnecessary or incorrect treatments. Furthermore, there are no histological grading systems developed specifically for AIH; at present the modified Ishak histological activity index[137] is commonly applied, but this does not reflect all of the features of AIH. AIH-specific histological scoring will be important for validated histological end points in future clinical trials in AIH[138]. In light of the low sensitivity and modest specificity of current serological tests in AIH[63] improvements in diagnostic tests in AIH are needed.

A range of questions remain open for variant syndromes, including whether these represent distinct pathological entities from their singular forms, whether the immune-mediated liver diseases exist on a continuum with overlap occurring in the middle, which factors predispose to variant syndromes and the optimal diagnostic criteria and management approaches. Due to the rarity and heterogeneity of these conditions these will be challenging to answer but clinicians must maintain a high index of suspicion to identify overlap syndromes, especially in patients with atypical presentations or responses to therapy.

Management

Despite seemingly efficacious treatments for AIH, real world response rates appear low; in a cross-sectional study of over 1200 patients in the United Kingdom (UK) less than 60% of patients were in remission, with disparity in remission rates between transplant and non-transplant centres (62% vs 55%, respectively) and 29 different treatment regimens reported[139]. There is also highly variable practice in the starting dose of steroids for induction of remission, the use of budesonide and the selection of second and third line agents in AIH[95,100]. These observations suggest a lack of uniformity in clinicians' approach and in the optimisation of therapy, which is likely to adversely impact on patient experience and outcomes and on the ability to pool data relating to third-line treatments. It will be important going forward to address these concerns to provide equitable and highly effective treatment to patients.

A significant proportion of patients have insufficient responses to current immunosuppressive regimens. Therefore, biomarkers allowing stratification or identification of (non)responders are much needed to enable prompt switches, escalation or de-escalation of medication to minimise futile treatment, treatment toxicity and uncontrolled disease. This is especially important, for example, in the setting of AS-AIH, where infection following corticosteroids could preclude life-saving emergency liver transplantation[67].

The high burden of side effects and the negative impact on quality of life of patients with AIH demonstrates the need for strategies to minimize corticosteroid exposure and for corticosteroid-free regimens in the future, as in other autoimmune diseases where chronic corticosteroid treatment has been progressively removed from standard management[140–142].

Quality of life

There are no validated patient reported outcome measures for AIH, meaning that quality of life assessment in AIH is reliant upon generic tools. These have demonstrated depressive disorders are present at significantly greater rates than in the general population and overall health-related quality of life and health utility are significantly impaired in adults and children[121,143–145]. There is clearly a need for an AIH specific patient reported outcome measure and prospective studies to accurately characterise

the impact of AIH and treatment on patients' quality of life, to determine rational, patient focussed endpoints for clinical trials and to test interventions to improve quality of life, such as treatments for depression and fatigue.

Aetiopathogenesis

The aetiology of AIH remains obscure; whilst certain environmental triggers have been described, for the majority of patients the specific triggering event remains undetermined. Furthermore, a single unifying target antigen, if one truly exists, remains elusive. An understanding of the mechanism of disease onset, propagation and target antigens may provide novel, rationalised treatment targets.

Another challenge is the need for representative animal models to explore the immunology and mechanism of AIH. Although multiple animal models of immuno-inflammatory hepatitis exist, they poorly represent human disease[146].

Unbiased assessment of the genetic contribution to AIH is limited to a single GWAS study in Northern European populations[147]; validation of these findings, extension to other populations and use of whole-genome sequencing techniques may lead to a better understanding of the genetic basis of AIH, again potentially providing opportunities for risk stratification, prognostication and mechanistic understanding and therapeutic targets[148].

Disease research networks

Being a rare disease has a significant impact on research in to AIH. Recruitment to trials may be hampered and, as demonstrated by many of the studies in AIH, research cohorts are small and frequently drawn from specialist centres which makes generalization of outcomes and treatment approaches to the wider population more challenging. However, there have been significant advances over the recent years. UK-AIH (www.uk-aih.com) is a multicentre research platform based in the UK that holds clinical and outcome data and biological samples from over 1000 patients from specialist and general hospitals. R-Liver is a multicentre prospective international registry including patients with autoimmune liver disease (https://rare-liver.eu/activities/registry), which promises to provide an invaluable resource in

AIH research. Pooling of resources and engagement of patients in multi-centre, multi-national research collaborations will be pivotal to ensure adequately powered studies in AIH.

Patient voice, agenda and delivery of care

Central to addressing the unmet needs in AIH with be determining the research and clinical agendas and models for delivery of care that are most relevant to patients. It is essential that research agenda is informed by the needs of patients so it is relevant and encourages patient engagement with research programmes. Patient representatives should be involved in planning research, approaches to care delivery and defining interventions and end-points in research trials. Organizations like the European Reference Network, amongst others, have patient representatives embedded within their structure.

The optimum model of care for patients' needs to be determined and may be differ between individual patient groups, healthcare settings and nations. General principles of personalised, proactive care are appropriate and patient preferences for, for example, remote monitoring, the use of communications technology, community vs specialised clinic-based care need to be considered. Multi-disciplinary management with doctors, specialist nurses and other allied health professionals such as psychologists and dieticians and access to other specialists are important.

Future treatment paradigms

A range of novel therapies are being actively considered in AIH. The current treatment paradigm of induction of remission with high dose corticosteroids and long-term maintenance with daily dosing of immunosuppressive drugs is problematic due to side effects from medication, low likelihood of long term treatment free remission and the proportion of patients who have insufficient response to current standard of care approaches. There is therefore interest in novel treatments which may either reduce dosing frequency, improve clinical outcomes or restore self-tolerance, enabling long term remission of disease[98].

As discussed above, there remain unanswered questions regarding the optimization of current first line therapies, such as the role of budesonide, dose optimisation of AZA and the use of allopurinol, alternative thiopurines, and optimum second and third line therapies in those intolerant or unresponsive to first line treatments. In addition to the development of these approaches, several novel drugs or treatment strategies may become available over the coming years that may alter treatment landscape in AIH.

There is an ongoing phase II, multi-centre, placebo-controlled trial of Ianalumab, an anti-B cell-activating factor of the tumour necrosis family (anti-BAFF) receptor antibody in patients intolerant of or with insufficient biochemical response to AZA and corticosteroids (ClinicalTrials.gov: NCT03217422). BAFF is an important survival signal for B cells[149], which due to the presence of circulating auto-antibodies, increased IgG and plasma cell infiltrate in the liver are thought to be important in the pathogenesis of AIH. If this proves to be an efficacious treatment, it will provide an alternative treatment option for patients, with lower dosing frequency and possibly reduced corticosteroid requirements.

Interest in cellular therapies to modify immune responses in allo- and auto-immune conditions has developed over the years. There is evidence that there may a defect in the function or balance of Treg and conventional T cells in AIH[150]. Strategies to enhance Treg function include low dose IL2 therapy, which selectively enhances Treg function compared to pro-inflammatory conventional T cells, and the *ex vivo* expansion and re-infusion of Treg to patients. Early evidence for efficacy of low dose IL2 in expanding Treg populations and reducing serum transaminases in AIH has been reported in a few

cases[151,152] and the feasibility of Treg expansion and re-transfusion with homing of Treg to the liver in AIH patients has been reported[153]. Other strategies being explored are to enhance regulatory immune responses by infusion of tolerogenic antigen presenting cells[154] and a trial is underway exploring the efficacy of mesenchymal stromal cells, which exert immunoregulatory effects on both the innate and adaptive immune systems, in patients with AIH or PSC (ClinicalTrials.gov:NCT02997878). The aim of all these approaches is to restore the balance of native immunoregulatory mechanisms and potentially restore immune tolerance. The hope would be that these techniques may even enable long term, drug-free remission or minimization the pharmacological burden upon patients.

As our understanding of the mechanisms of autoimmunity has evolved a host of new drugs targeting different loci in the immune response has become available to treat a range of autoimmune conditions. It is entirely conceivable that these drugs will be effective in suppressing immune responses in AIH and have potential as novel treatments for AIH[98,155]. It is likely that the treatments available for AIH will evolve over the coming decade and international collaboration in trials will be essential.

Conclusions

AIH is an archetypal, single organ autoimmune disorder. Despite well-established diagnostic criteria and effective treatments for AIH, there remain significant unmet needs and impact on quality of life and long term survival. However, as our understanding of the clinical features and aetiopathogenesis of the condition has advanced, diagnostic and clinical management protocols have evolved. With the changing treatment landscape with novel approaches in first line through to experimental therapies, improved care delivery for patients with AIH should be seen.

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Notes

Conflicts of interest The authors declare no conflicts of interest.

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Authors' contributions Alessio Gerussi and Neil Halliday reviewed the literature and drafted the manuscript. All authors read and approved the final version of the manuscript.

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Tables

	Features	Points received in the score
Typical AIH	• Interface hepatitis • Emperipolesis • Hepatic rosette formation	2
Compatible with AIH	Any combination of the previous without all the features present	1
Atypical Histology	Signs of other diagnosis	0

Table 1

Autoantibody	Target Antigen	Clinical context
ANA	Nuclear antigens: histones, chromatin, DNA	**Type 1 AIH**
Anti-SMA	Smooth muscle cytoskeleton components	**Type 1 AIH**
Anti-LKM1	Cytochrome P450 2D6	**Type 2 AIH**
Anti-F actin	Filamentous actin	Type 1 AIH (**More specific, less sensitive than anti-SMA for type 1 AIH**)
Anti-Liver Cytosol-1 (LC1)	Forminino-transferase cyclodeaminase	Type 2 AIH Associated with severe disease
pANCA	Peri-nuclear antigen. Atypical peripheral anti-nuclear neutrophil antibody (pANNA) pattern	Type 1 AIH
Anti-asialoglycoprotein receptor antibodies	Hepatocyte specific cell surface receptor	Not specific to AIH but associated with disease severity
LKM-3	Cytochrome P450 1A2	Type 2 AIH
Anti-Soluble liver antigen/liver-pancreas antigen	Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase	Associated with severe disease and relapse. **Highly specific for AIH**

Table 2

Autoimmune Hepatitis
• Serum ALT >5 x upper limit of normal
• Serum IgG >2 x upper limit of normal, or positive anti-SMA
• At least moderate peri-portal or periseptal lymphocytic piecemeal necrosis on biopsy
Primary Biliary Cholangitis
• ALP >2 x upper limit of normal or γGT >5 x upper limit of normal
• Positive AMA
• Florid bile duct lesion on biopsy

Table 3

Captions

Table 1 Histological items in Simplified Diagnostic Criteria
Adapted from Hennes et al[156].
Abbreviations: AIH-Autoimmune Hepatitis.

Table 2 . Autoantibodies in Autoimmune Hepatitis. Cardinal antibodies in bold.
Abbreviations: AIH – Autoimmune Hepatitis, ANA–antinuclear antibody, ANCA- Anti-neutrophil cytoplasmic antibodies, anti-SMA–anti-smooth muscle antibody, DNA- deoxyribonucleic acid, LKM–Liver-Kidney Microsomal, RNA- Ribonucleic acid.

Table 3 . Paris criteria for the diagnosis of Autoimmune Hepatitis-Primary Biliary Cholangitis overlap[157].
Requires the presence of 2 of 3 major diagnostic criteria for each of AIH and PBC, which must include the presence of interface hepatitis.
Abbreviations: ALT–alanine transaminase, IgG–immunoglobulin G, SMA–smooth muscle antibody, ALP–alkaline phosphatase, γGT–gamma-glutamyl transferase, AMA–antimitochondrial antibody.

Figure 1: Suggested Simplified Algorithm for the Management of Autoimmune Hepatitis (adapted from EASL guidelines 2015 and AASLD guidelines 2020)
Abbreviations: IV – intravenous, TPMT - thiopurine methylytransferase activity, LFTs – liver function tests,

Figure 2: Unmet Needs in Autoimmune Hepatitis
Abbreviations: AIH – Autoimmune Hepatitis, AZA – Azathioprine, GWAS – Genome-Wide Association Study, IL-2 – Interleukin 2, Treg – T regulatory lymphocytes, BAFF – B-cell activating factor, R-LIVER – Rare-LIVER registry, UK-AIH – United Kingdom AIH.

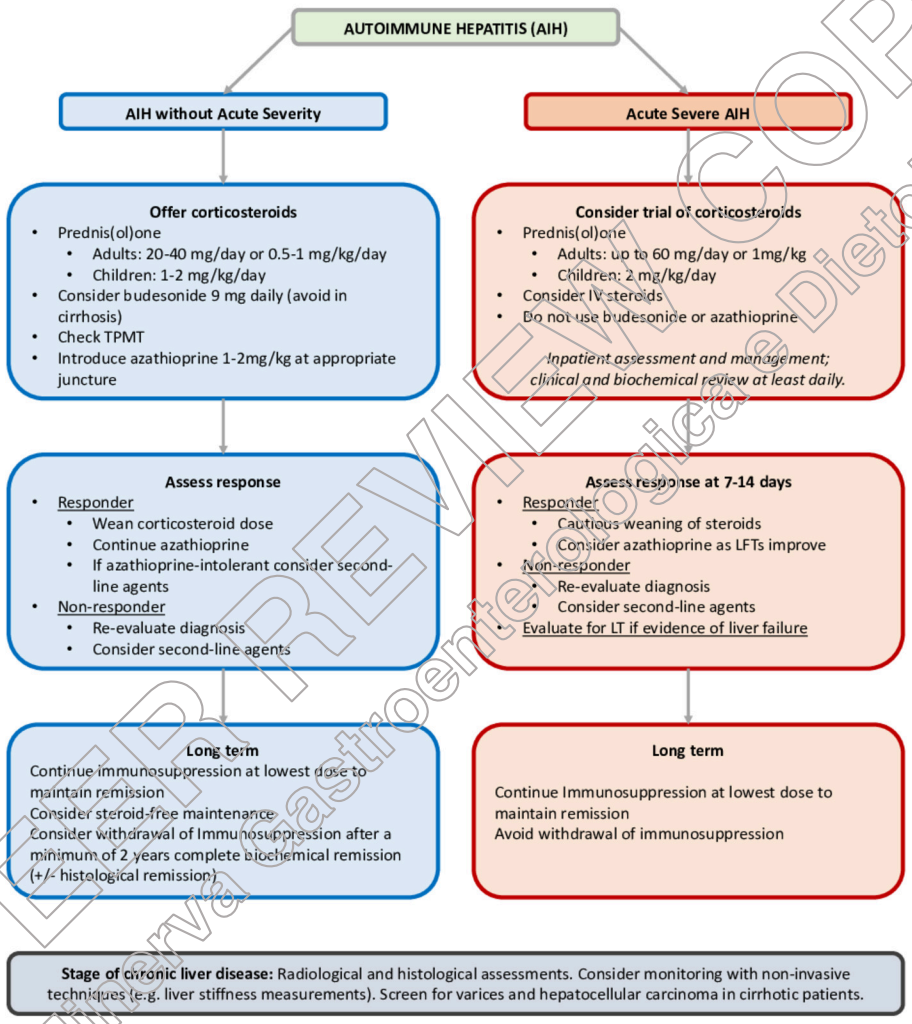

FIGURE 1

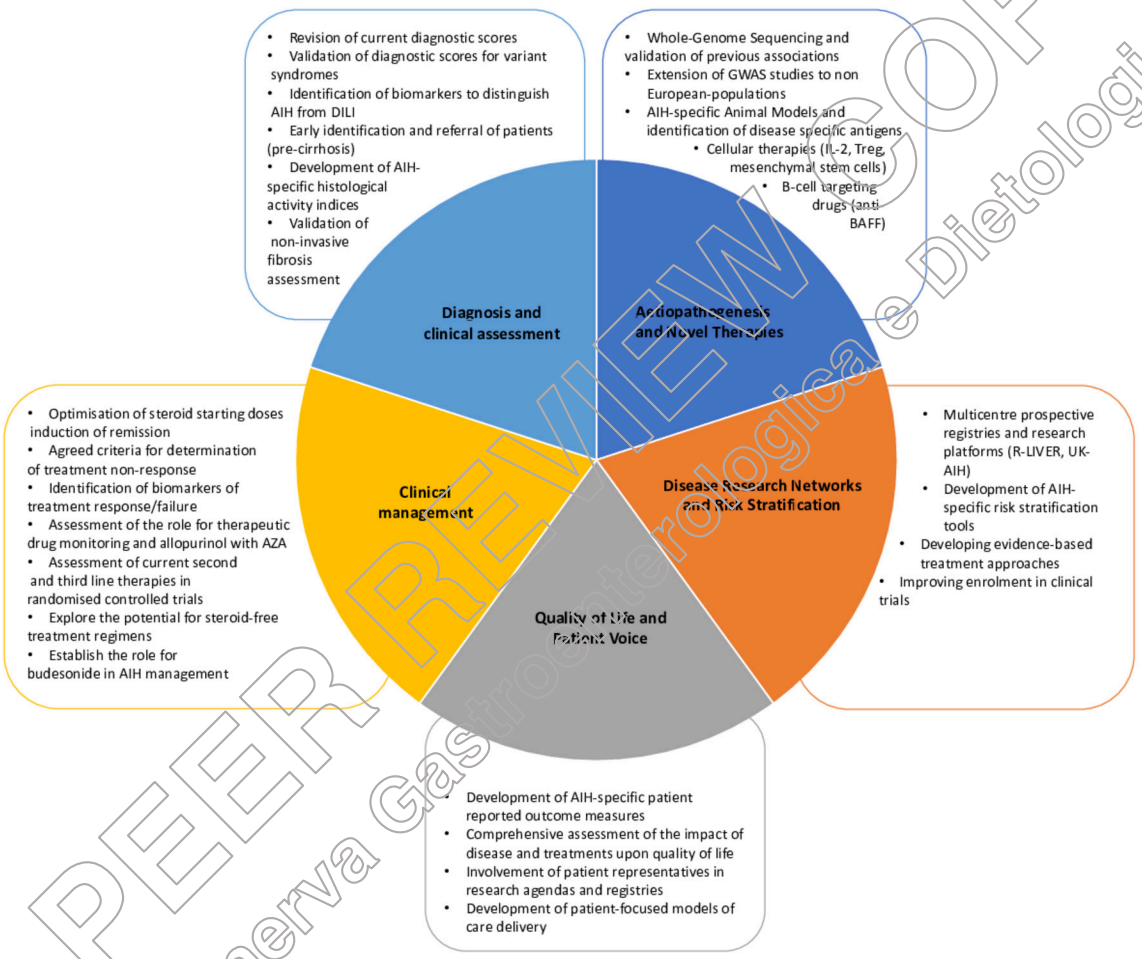

FIGURE 2