

Diagnosis and management of autoimmune hepatitis

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Abstract

Autoimmune hepatitis is an inflammatory disease of the liver of unknown cause that may progress to liver cirrhosis and end stage liver failure if diagnosis is overlooked and treatment delayed. The clinical presentation is often that of acute hepatitis, sometimes very severe; less frequently, it can be insidious or completely asymptomatic. The disease can affect people of any age and is more common in women; its incidence and prevalence seem to be on the rise worldwide. An abnormal immune response targeting liver autoantigens and inducing persistent and self-perpetuating liver inflammation is the pathogenic mechanism of the disease. A specific set of autoantibodies, increased IgG concentrations, and histological demonstration of interface hepatitis and periportal necrosis are the diagnostic hallmarks of autoimmune hepatitis. Prompt response to treatment with corticosteroids and other immunomodulatory drugs is almost universal and supports the diagnosis. The aims of treatment are to induce and maintain long term remission of liver inflammation. Treatment can often even reverse liver fibrosis, thus preventing progression to advanced cirrhosis and its complications. Most patients need lifelong maintenance therapy, and repeated follow-up in experienced hands improves the quality of care and quality of life for affected patients.

Introduction

Autoimmune hepatitis is a rare immune mediated inflammatory disease of the liver characterized by circulating autoantibodies, increased concentration of IgG, and distinctive histological features.¹ The origin of the disease is presumed to be a loss of immunologic tolerance against hepatocytes induced by environmental factors in genetically predisposed people, possibly through “molecular mimicry.”² Originally defined as “lupoid hepatitis” and affecting young women,³ it is now considered to be a disease affecting both sexes and all ages and races worldwide.⁴ The diagnosis of autoimmune hepatitis remains challenging because of the wide age range at presentation, heterogeneous serologic markers, and diverse clinical picture, ranging from asymptomatic disease to fulminant hepatic failure.⁵ The aim of treatment is to induce remission, defined as normalization of aminotransferases and IgG at six months,⁶ and to maintain remission thereafter. Whether normalized biochemical markers are a reliable proxy of resolved histological activity is uncertain.⁷ Early randomized trials showed that steroid treatment improves survival and that the rate of maintenance of remission is significantly higher when azathioprine is added.⁸⁻¹² Approximately 10-20% of patients with autoimmune hepatitis do not achieve remission with the standard treatment

or develop severe side effects necessitating discontinuation of treatment.¹³ Second line treatments are well defined, whereas options for third line therapies are quite heterogeneous.¹⁴ For non-responder patients progressing to liver failure, the rescue option is liver transplantation.¹⁵

This review summarizes current knowledge in diagnosis and treatment of autoimmune hepatitis, with special focus on the patient's perspective. It is intended for specialists and academics, as well as for non-specialist hepatologists and gastroenterologists.

Sources and selection criteria

We searched PubMed for English language articles published between 1 January 2012 and 1 June 2022, using the keywords “autoimmune hepatitis”, “diagnosis”, “clinical phenotype”, and “treatment”. We manually reviewed the results and included only English language published studies, guidelines, randomized controlled trials, systematic reviews, and meta-analyses. We did an additional search of the Cochrane Library by using the search term “autoimmune hepatitis and treatment”. Finally, we included additional seminal papers on autoimmune hepatitis not previously identified through PubMed or Cochrane Reviews on the basis of a review of current guidelines and landmark journal articles. The PubMed search retrieved 1270 papers, but after applying the

exclusion criteria through the manual review we reviewed 286 full length articles and six guidelines. The Cochrane search retrieved no pertinent article.

Epidemiology and clinical presentation of autoimmune hepatitis

Epidemiology

Autoimmune hepatitis can affect all ages and all populations, regardless of race and ethnicity.¹⁶ The pooled worldwide annual incidence and prevalence are 1.37 and 17.44 per 100 000 people, respectively. Pooled annual incidences for Asian, European, and American populations are 1.31, 1.37, and 1.00 per 100 000. Pooled prevalences for Asian, European, and American populations are 12.99, 19.44, and 22.80 per 100 000, respectively.¹⁷ The lower prevalence in Asian in comparison with European and American populations can be explained by the different genetic background, as European and North American people are mainly white, with a higher frequency of HLA DR3 and DR4 in patients with autoimmune hepatitis. In addition, environmental factors such as better living conditions, changes in lifestyle habits, and diet remodulate the intestinal microbiome, which in turn affects the immune system and the gut-liver axis.¹⁸ In keeping with the increasing rate of autoimmune phenomena,¹⁹ autoimmune hepatitis seems to be on the rise according to population based studies conducted in Denmark, where incidence increased from 1.37 in 1994 to 2.33 in 2014,²⁰ and in England, where the incidence doubled from 1.27 to 2.56 during the 1997-2015 period.²¹ In addition, a more northerly latitude is associated with an increased incidence of autoimmune hepatitis in the UK, possibly owing to lower sun exposure and the consequent lack of vitamin D.²²

Clinical presentation

The clinical phenotype of the disease can be extremely heterogeneous, from asymptomatic,²³ mostly observed in patients with concomitant autoimmune conditions,^{24 25} to fulminant hepatitis leading to liver failure, in both adult and pediatric settings.^{5 26-28} Most patients are in their second or fifth/sixth decade, and three quarters are women. Clinical presentation of autoimmune hepatitis is generally expressed in three patterns: acute onset, insidious onset, and asymptomatic onset.^{4 29} These patterns are outlined below.

Acute onset of autoimmune hepatitis has become the most frequent pattern worldwide, not only in adults but also in children and adolescents.^{27 30-34} It presents with transaminase concentrations at least five to 10 times the upper limit of normal, often with jaundice and sometimes with prolonged international normalized ratio. After all other causes of liver injury have been excluded, the diagnosis is supported by presence of increased concentrations of IgG, typical autoantibodies, such as antinuclear antibodies, smooth muscle antibodies (SMA), liver/kidney microsomal antibody type 1 (anti-LKM1), liver cytosol antibody type 1 (anti-LC1), and soluble liver antigen/liver pancreas antibodies (anti-SLA/

LP), and liver histology with features of interface hepatitis. A small number of patients present with acute severe/subfulminant hepatitis, which can sometimes progress to acute liver failure.^{5 35 36} This rare type of patient should be quickly referred to a liver transplant center.

Insidious onset is characterized by non-specific symptoms such as fatigue, arthralgias, malaise, amenorrhea, and, in a small proportion of cases, signs and symptoms of hepatic cirrhosis.^{28 29 37-39}

With asymptomatic onset, the patient does not present liver related signs or symptoms and is assessed when altered liver function tests have emerged accidentally or when other medical conditions are being investigated, particularly extra-hepatic autoimmune disorders, such as thyroid disease, celiac disease, and rheumatologic conditions.^{23-25 40-42}

Special patient populations with autoimmune hepatitis

Autoimmune hepatitis manifests itself differently in different patient populations, which in turn may have different needs and require a differentiated approach.

Older and pediatric patients

Long term cohorts indicate that the median age at diagnosis of autoimmune hepatitis is slowly but constantly increasing worldwide.^{22 29 43 44} Autoimmune hepatitis can occur in people of any age and race and is not restricted to young women. The diagnosis should not be overlooked in the older population,^{39 44-46} in whom excluding drug induced liver injury may be particularly challenging. An interesting feature of autoimmune hepatitis diagnosed in the older population is the more benign course, the higher rate of complete response to treatment, and an overall better prognosis in comparison with patients whose autoimmune hepatitis is diagnosed at a younger age.⁴⁴⁻⁴⁹

On the other hand, autoimmune hepatitis in children is quite rare, with incidence rates as low as 0.4 per 100 000 in western populations.⁵⁰ Autoimmune hepatitis in children has historically been described as potentially very severe or even fulminant.^{27 51-54} The autoantibody profile in the pediatric/adolescent setting is broader than in adults. During follow-up it may also change significantly, switching from isolated anti-LC1 to isolated antinuclear antibodies, for example, passing through a phase of concomitant anti-LC1 and SMA positivity.⁵⁵ In this regard, notwithstanding the relevant differences between pediatric and adult/older patients with autoimmune hepatitis,^{48 56} classifying autoimmune hepatitis in different subtypes according to the autoantibody profile,⁵⁷ which can be transient and unstable,⁵⁵ may seem confusing and purposeless.

Adolescents with autoimmune hepatitis and transition from child centered to adult healthcare system

This is a delicate phase for patients and their families, who are both at the center of the relevant change, and a challenge for physicians coordinating

the process. Regarding children, the delivery of care is fundamentally family centered, whereas an adult patient is autonomous and fully responsible. During transition, adolescents are no longer expected to rely on parents and parents are expected to step back and allow for independent decisions. Overprotection and inadequate support can both be detrimental and could lead to unsuccessful transition.

In the meantime, generic programs can be used across all specialties and be adapted as needed.⁵⁸⁻⁶⁰ The principal aims of these programs are to empower young people to take control of their long term conditions and to equip them with the necessary skills and knowledge to manage their own healthcare.

Most of these programs are achieved through a series of questionnaires. Specific guidelines for patients with autoimmune hepatitis during the transition phase have not been developed so far and are urgently needed.⁶¹⁻⁶³

Pregnant patients

Many female patients with autoimmune hepatitis at childbearing age request information on pregnancy in relation to their hepatic condition. In general, pregnancy and childbirth seem to be safe for both mother and child.⁶⁴⁻⁶⁹ If not properly controlled, however, autoimmune hepatitis can flare up during pregnancy, and this is associated with a high rate of



Fig 1 | Cellular and molecular mechanisms of autoimmune hepatitis. Factors proposed to alter the risk of developing autoimmune hepatitis, presented by category. Many of these factors are speculative or unconfirmed (including *AIRE*, *FAS/FASL*, *CTLA4*, and *GATA2* mutations outside of specific syndromes), but the HLA-D allele, *SH2B3* variants, female sex, age, pregnancy, and exposure to several drugs have been confirmed to be associated with the development of autoimmune hepatitis. *AIRE*=autoimmune regulator; *CMV*=cytomegalovirus; *CTLA4*=cytotoxic T lymphocyte antigen 4; *EBV*=Epstein-Barr virus; *FAS/FASL*=CD95 and CD95 ligand; *GATA2*=GATA binding factor type 2; *HAV*=hepatitis A virus; *HCV*=hepatitis C virus; *HEV*=hepatitis E virus; *NAFLD*=non-alcoholic fatty liver disease; *PD-1/PD-L1*=programmed death receptor 1/programmed death receptor ligand 1; *SH2B3*=gene encoding adaptor protein also known as Lnk; *Tr1*=type 1 regulatory T cell; *Treg*=regulatory T cell. Adapted from Webb GJ, et al, *Annu Rev Pathol* 2018⁸²

fetal and maternal complications within the range of 10-20%. Pregnancy should be initiated when the disease is in stable and persistent remission,⁴ and immunosuppression with azathioprine should be neither reduced nor suspended, as its teratogenic potential in animals is not observed in humans. In contrast to azathioprine, mycophenolate mofetil is teratogenic for humans and must be replaced with steroid monotherapy in patients who cannot tolerate azathioprine, leaving ciclosporin or tacrolimus as the last option.⁶⁹ The previous suggestion that steroids may induce oral-facial clefts and adverse pregnancy outcomes (preterm births, pre-eclampsia, low birth weight) has not been confirmed.⁶⁹ Loss of biochemical remission is quite common after delivery, so a course of steroids at increased dosage is suggested for a short period of time.⁶⁹

Patients presenting with variant syndromes

A very small proportion of patients with autoimmune hepatitis may show prominent cholestatic features, suggesting the coexistence of overlapping primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). According to the Paris criteria,⁷⁰ to identify autoimmune hepatitis overlapping with PBC, two of the following three PBC criteria should be met: serum alkaline phosphatase concentration at least twofold the upper limit of normal or serum γ -glutamyl transferase concentration at least fivefold the upper limit of normal, positivity for antimitochondrial antibodies, and florid bile duct lesions on liver histology. To diagnose autoimmune hepatitis-PSC overlap syndrome, also known as autoimmune sclerosing cholangitis in children,⁵³ all the following criteria must be met: presence of typical features of autoimmune hepatitis,¹ absence of antimitochondrial antibodies, and evidence of large duct PSC by endoscopic or magnetic resonance cholangiography or evidence of small duct PSC on liver histology. Testing for autoimmune hepatitis-PSC overlap syndrome should be considered in those patients with autoimmune hepatitis who also have inflammatory bowel disease, especially ulcerative colitis, or who have unexplained cholestatic laboratory findings. It should also be considered in patients who do not respond to conventional immunosuppressive therapy.

Quality of life

Universally recognized treatment endpoints in autoimmune hepatitis include induction and

Box 1: Causes of liver injury

- Viral hepatitis (hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, Epstein-Barr virus, cytomegalovirus)
- Drugs, including over-the-counter medications
- Herbal remedies
- Wilson disease
- Hemochromatosis
- Non-alcoholic steato-hepatitis

maintenance of biochemical and histological remission. Despite this progress, a clear need still exists for better treatment options and expanded endpoints in every aspect of autoimmune hepatitis.⁷¹ First line and second line treatments are characterized by several mostly dosage dependent side effects that may greatly affect quality of life, even when biochemical and histological remission are reached.⁷²⁻⁷³ This has a particular impact on children and adolescents, whose adherence to treatment is often lower.⁴⁹ High dose steroids can cause metabolic and neuropsychiatric complications, and, in the long term, steroid induced osteoporosis is a major comorbidity affecting quality of life. In addition, azathioprine increases the risk of hematologic malignancy and skin cancer.⁷⁴ Fatigue, anxiety, depression, and a globally reduced quality of life are reported by the vast majority of patients with autoimmune hepatitis.⁷⁵⁻⁷⁷ Depression seems to be partly associated with prolonged steroid use, but the frequency and degree of depression in autoimmune hepatitis suggest additional factors influencing the decreased quality of life.⁷⁸ Being cared for in a referral center and having a trustful doctor-patient relationship were recently shown to have a strong positive influence on the overall quality of life⁷⁹—a clearly modifiable factor that should receive more attention and strongly argues for a structured care system allowing access to expert care for all patients with autoimmune hepatitis, as well as quality control measures of the care delivered.⁸⁰

Future interventional studies need to tackle these aspects of the disease as endpoints in a systematic way. They should consider the perceived wellbeing of patients with autoimmune hepatitis as a whole and not limit the focus to the hepatological aspects of the disease.

Pathogenesis

Although the precise pathophysiological mechanisms leading to chronic liver inflammation and progression of the disease are still elusive, several relevant areas have been studied extensively. These include genetics and epigenetics, abnormal autoimmune regulatory mechanisms, and environmental trigger factors and are shown in figure 1 and outlined below.⁸¹⁻⁸²

Genetics and epigenetics

The prominent predisposing role of HLA alleles, especially HLA-DR3 and HLA-DR4, has been reported extensively³⁸; however, predisposing HLA genes may vary among different ethnicities and geographic regions.⁸³ In addition, epigenetic factors that alter gene expression without changing the nucleotide sequence may also contribute to the clinical expression and phenotype of the disease.⁸⁴ Multiple hypo-methylated genes have been described in the CD4 positive and CD19 positive T lymphocytes of patients with autoimmune hepatitis,⁸⁵ and the circulating micro-ribonucleic acids miR-21 and miR-122 correlate with laboratory and histological features of liver inflammation.⁸⁶ Moreover, outside the

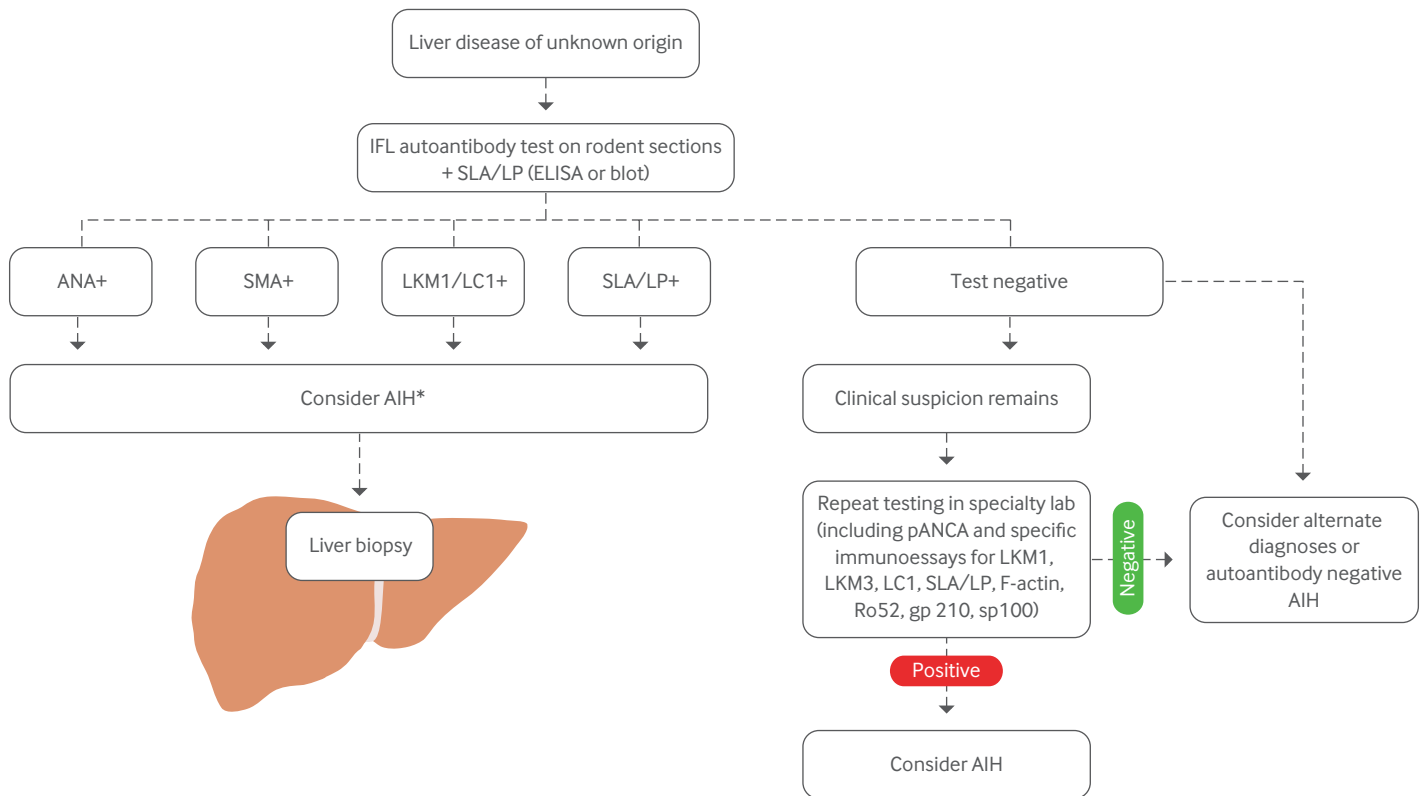


Fig 2 | Algorithm for patients with possible autoimmune hepatitis (AIH). ANA=antinuclear antibodies; ELISA=enzyme linked immunosorbent assay; anti-LC1=liver cytosol antibody type 2; anti-LKM1=liver/kidney microsomal antibody type 1; pANCA=peripheral antineutrophil cytoplasmic antibodies; anti-SLA/LP=soluble liver antigen/liver-pancreas antibodies; SMA=smooth muscle antibodies. Adapted from European Association for the Study of the Liver, *J Hepatol* 2015¹

major histocompatibility complex, single nucleotide polymorphisms concerning pro-inflammatory as well as regulatory pathways have also been described in autoimmune hepatitis, affecting genes such as those for tumor necrosis factor, CTLA-4/CD28, FAS, TGF 1, and interleukin-4.⁸³

Abnormal immune regulation

The imbalance between pro-inflammatory mechanisms and regulatory ones is presumed to play a pivotal role in the pathogenesis of autoimmune diseases in general and autoimmune hepatitis in

particular.^{87 88} The activities of the regulatory cells, Th1 cells, Th17/Th22 cells, activated macrophages, complement, and natural killer cells are all interconnected and finely tuned, and when such a system becomes dysfunctional, the autoimmune disorder may ensue.⁸⁹ The number of regulatory T cells is reduced and their function is impaired, a scenario in which cytotoxic cells such as Th17 are let loose to initiate and perpetuate liver injury without proper control.⁸⁹ The intrahepatic environment seems to be particularly skewed toward a pro-inflammatory milieu that favors recruitment and activation of inflammatory and potentially autoreactive T cells, whereas the regulatory components of the immune system are largely silenced.⁸⁷

Environmental trigger factors

Exposure to external factors is considered necessary to trigger the autoimmune reaction against liver structures, supposedly via a molecular mimicry based mechanism. Common viral infections such as hepatitis viruses, measles virus, cytomegalovirus, Epstein-Barr virus, and varicella zoster virus are potential inciting factors.^{2 90} Several drugs have been associated with the development of a condition resembling autoimmune hepatitis. Historically, nitrofurantoin and minocycline have been associated with induction of autoimmune hepatitis. Other drugs and herbal remedies have also been occasionally

Box 2: Negative prognostic factors in autoimmune hepatitis

- Cirrhosis at onset
- Young age at onset
- Repeated relapses of active disease on drug withdrawal
- Variant syndromes (autoimmune hepatitis-PSC, autoimmune hepatitis-PBC) and concomitant liver disease (NASH/NAFLD)
 - Ethnicity (black race)
 - Vitamin D deficiency

NASH=non-alcoholic steato-hepatitis; NASFLD=non-alcoholic fatty liver disease; PBC=primary biliary cholangitis; PSC=primary sclerosing cholangitis

Table 1 | Simplified criteria for autoimmune hepatitis (AIH): update of serologic criteria

Variable	Cut-off	Points*
ANA or SMA/F-actin	Positive†	1
ANA or SMA/F-actin	Strongly positive‡	
Or anti-liver/kidney/microsomal antibody type 1	≥1:40	2
Or anti-soluble liver antigen antibody	Positive	
IgG	>Upper limit of normal	1
	>1.1 × upper limit of normal	2
Liver histology (with evidence of hepatitis)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2

ANA=antinuclear antibodies; F-actin=filamentous actin; IFT=indirect immunofluorescence; SMA=smooth muscle antibodies.

*Addition of points achieved (maximum 2 points for autoantibodies). ≥6 points=probable AIH; ≥7 points=definite AIH.

†IFT ≥1:40 when assessed on tissue sections; ≥1:80 or 1:160 for ANA when assessed on HEp-2 cells, depending on local standards; enzyme linked immunosorbent assay with locally established cut-offs.

‡IFT ≥1:80.

Adapted from Galaski J, et al, *J Hepatol* 2021.¹¹⁶

reported to induce autoimmune hepatitis, including oxypheinsatin, ornidazole, methyl dopa, diclofenac, interferon, atorvastatin, highly active antiretroviral treatment, and biologic agents such as infliximab, natalizumab, and adalimumab.⁹¹⁻⁹³ Vaccination has also been invoked as a possible trigger of the disease.⁹⁴⁻⁹⁷

The microbiome in autoimmune hepatitis

Alterations of the commensal microbiome and aberrant immune system activation by microbial signals, mainly via the gut-liver axis, are emerging in autoimmune hepatitis. *Veillonella*, *Klebsiella*, *Streptococcus*, and *Lactobacillus* are relatively increased in patients with autoimmune hepatitis.⁹⁸ Another study identified *Lachnospiraceae*, *Veillonella*, *Bacteroides*, *Roseburia*, and *Ruminococcaceae* as microbial biomarkers of autoimmune hepatitis.⁹⁹ In Egypt, *Faecalibacterium*, *Blautia*, *Streptococcus*, *Hemophilus*, *Bacteroides*, *Veillonella*, *Eubacterium*, *Lachnospiraceae*, and *Butyricoccus* were enriched in patients with autoimmune hepatitis, whereas *Prevotella*, *Parabacteroides*, and *Dilaster* were significantly reduced.¹⁰⁰ In addition to the increase of *Veillonella*, a disease specific decline in the relative abundance of *Bifidobacterium* was also observed in patients with autoimmune hepatitis.¹⁰¹ In addition, the oral microbiome is significantly different in autoimmune hepatitis, with enrichment of *Streptococcus*, *Veillonella*, and *Leptotrichia*.¹⁰² If these observations are confirmed and acquire pathogenetic relevance, probiotics or targeted dietary intervention to manipulate the composition of the microbiome might be considered as additional therapeutic strategies for autoimmune hepatitis.¹⁰³

Diagnosis

Diagnosing autoimmune hepatitis may be challenging because no clinical sign or symptom nor any single biochemical or histological finding is pathognomonic of the disease. Autoimmune hepatitis should be considered in the differential diagnosis of any patient with elevated liver enzymes and/or liver cirrhosis of unknown origin. Although careful

exclusion of all known causes of liver injury is needed (box 1),⁴ non-alcoholic steato-hepatitis (NASH) in combination with autoimmune hepatitis is seen increasingly, comorbidity of autoimmune hepatitis and hepatitis B virus is not uncommon in countries with high rates of hepatitis B virus infection, and most patients with autoimmune hepatitis, especially among the older population, are or have been taking some drugs with hepatotoxic potential. Concomitant causes of liver injury should not delay diagnosis and treatment of autoimmune hepatitis.

The diagnosis is based on a set of clinical, biochemical, serologic, and histological findings, such as high concentrations of aminotransferases, polyclonal hypergammaglobulinemia, high IgG, circulating autoantibodies, and periportal necrosis on histology.⁴ Figure 2 shows a case based algorithm for patients with suspected autoimmune hepatitis. Box 2 shows negative prognostic factors.

Diagnostic scoring systems for autoimmune hepatitis

The first scoring system for the diagnosis of autoimmune hepatitis was proposed in 1993,¹⁰⁴ revised in 1999,¹⁰⁵ and simplified in 2008 to assist and standardize the diagnostic process.¹⁰⁶ The 1993 score was rather cumbersome and, in addition to clinical, biochemical, histological, and genetic parameters, also assessed the response to treatment.¹⁰⁴ The revised 1999 score was still considered too complex and failed to differentiate between autoimmune hepatitis and cholestatic syndromes.^{107 108} The simplified scoring system is proposed as a practical and easy-to-use clinical tool, requiring only four simple variables: autoantibodies, hypergammaglobulinemia, histology, and exclusion of viral hepatitis.¹⁰⁶ A comparison between the revised and the simplified scoring systems highlighted the higher sensitivity (100% v 95%) of the former but the higher specificity (90% v 73%) and accuracy (92% v 82%) of the latter.¹⁰⁹⁻¹¹¹ The simplified scoring system is useful in excluding autoimmune hepatitis in patients with other conditions and concurrent immune features,^{112 113} but it fails to identify atypical cases^{109 110 112} and should always be used with clinical judgment.¹¹⁴

Autoantibodies

Autoantibodies are a hallmark of autoimmune hepatitis and have been the key components of all versions of the diagnostic scoring system,¹⁰⁴⁻¹⁰⁶ even though most of them are not disease specific. Indirect immunofluorescence on unfixed frozen rodent sections of liver, kidney, and stomach has been suggested as the test of choice to detect them.¹¹⁵ Indirect immunofluorescence for antinuclear antibodies on HEp-2 cells and evaluation of antinuclear antibodies and smooth muscle antibodies in enzyme linked immunosorbent assay (ELISA) based assays have recently been proposed as alternative tests.¹¹⁶ Table 1 shows the proposed implementation of these testing methods in the

simplified criteria for the diagnosis of autoimmune hepatitis.

The historical serologic subclassification of autoimmune hepatitis relied on the autoantibody profile: antinuclear antibodies and SMA as markers of type 1 autoimmune hepatitis and anti-liver-kidney microsomal antibody type 1 (anti-LKM1) and anti-liver-cytosol type 1 (anti-LC1) as markers of type 2 autoimmune hepatitis, almost exclusively diagnosed in children.¹ Approximately 15-20% of all patients with autoimmune hepatitis are positive for anti-soluble liver antigen/liver-pancreas (anti-SLA/LP) antibodies, characterized by high specificity (0.99) but low sensitivity (0.19) for autoimmune hepatitis.¹¹⁷ Anti-SLA/LP are detected by ELISA or immunochemical assays, but not by indirect immunofluorescence,¹¹⁸ and are often found associated with other autoantibodies, including antinuclear antibodies, SMA, anti-LKM1, and anti-LC1.¹¹⁹⁻¹²² Only sporadic patients show anti-SLA/LP as a unique serologic marker of autoimmune hepatitis.¹¹⁸ Anti-SLA/LP was originally associated with a severe phenotype of the disease,¹²³⁻¹²⁵ but its unfavorable prognostic significance is not

univocally recognized.^{120 122 126} Of note, anti-SLA/LP positive patients seem to be at higher risk of relapse and therefore more often need permanent immunosuppression.¹²⁶

Antimitochondrial antibodies, the serologic marker of PBC,¹²⁷ can be detected in a proportion of patients with typical autoimmune hepatitis without additional cholestatic features.^{128 129} Comparison of antimitochondrial antibody positive patients versus antimitochondrial antibody negative ones with autoimmune hepatitis failed to identify clinical, biochemical, or histological differences. None of the antimitochondrial antibody positive patients developed clinical or biochemical features of PBC during follow-up, and in sporadic patients antimitochondrial antibody was the only detectable serologic marker.¹³⁰

The subclassification of autoimmune hepatitis according to the autoantibody profile lacks major clinical value, even if associated with epidemiologic and genetic differences.^{51 131} The reason for this is that the clinical expression of the disease and the treatment schedule, response, and outcome—both in adults and in children—are substantially one and the same.^{57 132}

AIH treatment algorithm

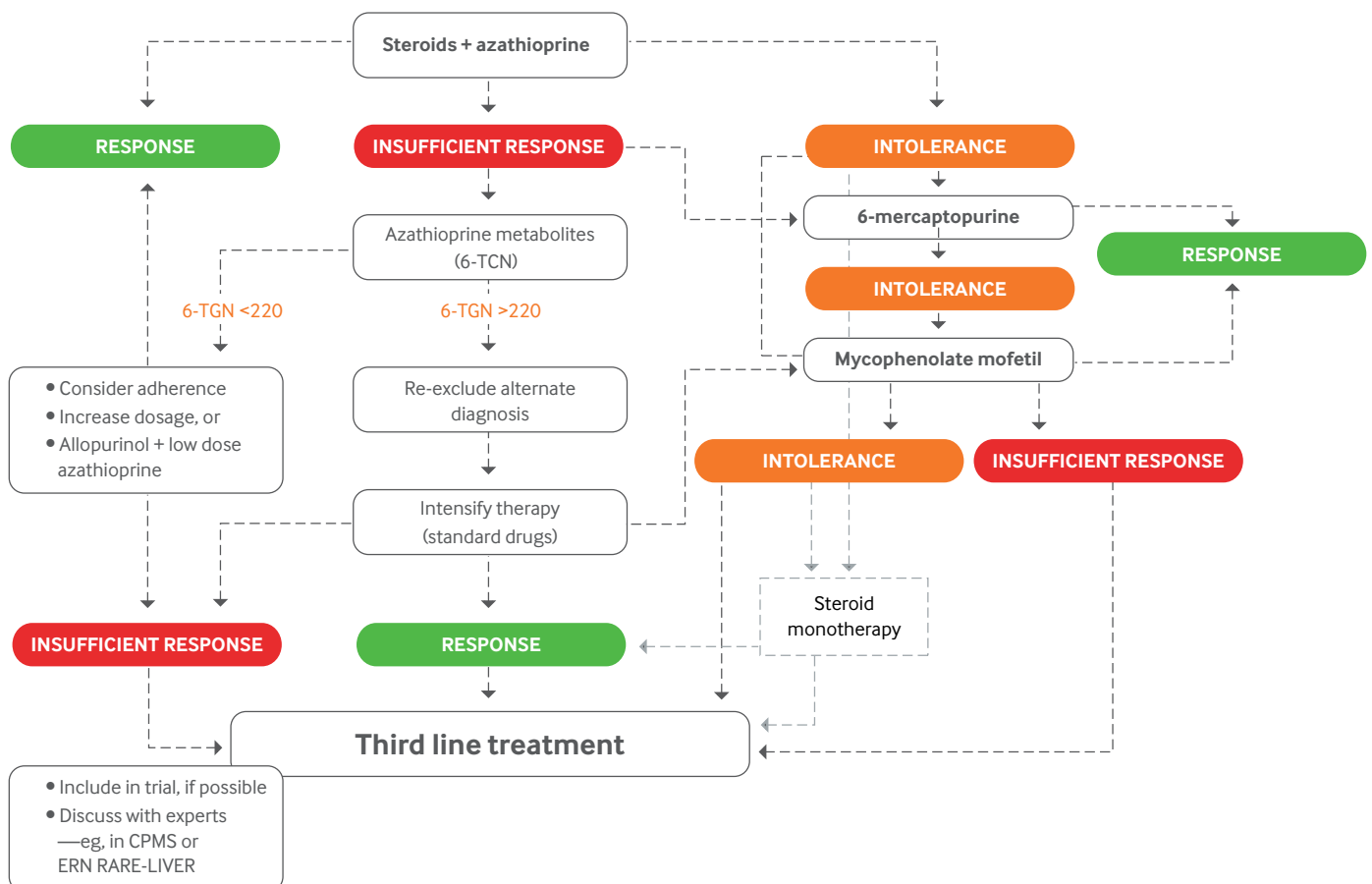


Fig 3 | Treatment algorithm for autoimmune hepatitis (AIH). 6-TGN=6-thioguananine; CPMS=clinical patient management system. Adapted from Lohse AW, et al, *J Hepatol* 2020¹⁴

Histology

Liver histology is mandatory for the diagnosis of autoimmune hepatitis. Assessing the degree of inflammatory activity such as interface and lobular inflammation, which is not reliably depicted by the increase in transaminase concentrations, and the degree of fibrosis is essential. It is also helpful in excluding other causes of liver disease.^{1 4 106 133} However, no single histological feature is specific or pathognomonic for autoimmune hepatitis.¹³⁴ To define histology as typical of autoimmune hepatitis, the International Autoimmune Hepatitis Group's simplified criteria require two out of three of the following features: interface lymphocytic hepatitis, emperipolesis, and hepatocellular rosettes.¹⁰⁶ Interface hepatitis, the histological hallmark of autoimmune hepatitis, is characterized by portal inflammation with dense plasma cell rich infiltrates extending beyond the limiting plate, is present in up to 98% of patients, and is usually more severe in autoimmune hepatitis than in viral hepatitis.¹³⁵ Emperipolesis and rosettes lack diagnostic specificity for autoimmune hepatitis, as they reflect inflammatory activity and the subsequent regeneration process rather than etiology.^{134 136}

A recent consensus proposes liver biopsy to be considered as:

- “Likely autoimmune hepatitis” if a portal lymphoplasmacytic infiltrate is present with at least one of the following two features: more than mild interface hepatitis or more than mild lobular hepatitis
- “Possible autoimmune hepatitis” if the two likely features are lacking in the absence of histological features suggestive of another disease or one or both of the two likely features are present in combination with histological features suggestive of another liver disease
- “Unlikely autoimmune hepatitis” if histological features suggestive of another liver disease are present and if likely features of autoimmune hepatitis are absent.¹³⁷

A real challenge in interpreting liver histology is when the biopsy is taken within the first three months in patients with acute onset of autoimmune hepatitis¹³⁸⁻¹⁴⁰: liver damage is predominant in the centrilobular area^{141 142} and transition from pericentral to portal-periportal hepatitis has been shown to occur only thereafter.¹⁴³ Centrilobular injury, which is observed in 29% of patients with autoimmune hepatitis and is the only finding in just 1-2%, seems to represent the early histological manifestation of the disease.^{144 145}

The role of imaging

Imaging has so far played a limited role in the management of autoimmune hepatitis, its main function being restricted to the assessment of liver complications of cirrhosis and screening for hepatocellular carcinoma. However, new technologies are opening up the potential of transforming imaging into a non-invasive tool to

assess and predict disease activity in patients with autoimmune hepatitis.¹⁴⁶

Several studies have shown a good degree of accuracy of imaging techniques in classifying cirrhosis and significant fibrosis.¹⁴⁷ Ultrasound elastography is a useful non-invasive tool for monitoring disease progression in patients being treated for autoimmune hepatitis, to assess residual inflammatory activity despite complete biochemical remission. However, hepatic inflammation has been identified as a potential confounder generating false positive results for liver stiffness.⁴ In patients with autoimmune hepatitis treated for less than three months, liver stiffness correlates better with histological grading than with staging. In patients treated for six months or longer, accuracy is excellent in the detection of advanced fibrosis.¹⁴⁸

Multiparametric magnetic resonance imaging (MRI) can generate quantitative information of clinical utility as a non-invasive tool for the diagnosis of liver diseases.¹⁴⁹ Iron corrected T1 is a reliable multiparametric MRI measurement of fibro-inflammatory activity, predictive of clinical outcome, with low inter-observer variability and good correlation with liver histology.^{150 151} Monitoring the inflammatory response is a key element in managing autoimmune hepatitis, and liver biopsy is still considered essential to decide on drug withdrawal.⁴ Multiparametric liver MRI, a sort of “virtual biopsy” with the advantage of a panoramic non-invasive technique, will be particularly useful to evaluate autoimmune hepatitis, which is heterogeneously distributed across the liver. In particular, such a technique has the potential to inform risk stratification of patients and to assist in the decision to withdraw treatment, a pivotal step in the management of autoimmune hepatitis.¹⁵²

Differential diagnosis of autoimmune hepatitis and drug induced liver injury

The increased frequency of autoimmune hepatitis with acute onset highlights the problem of the differential diagnosis between classic autoimmune hepatitis and drug induced liver injury (DILI) with autoimmune features.¹⁵³ Both conditions frequently exhibit the same clinical, biochemical, and serologic phenotype. The usual approach to differentiate between autoimmune hepatitis and DILI is essentially clinical: discontinuation of the offending drug is the obvious choice in DILI, and spontaneous improvement is expected to occur shortly afterwards. Steroid therapy is warranted only for symptomatic or severe cases of DILI; relapse after steroid withdrawal usually does not occur. The absence of disease relapse after steroid withdrawal distinguishes DILI from classic autoimmune hepatitis.¹⁵⁴ Liver histology is not particularly helpful in differentiating between DILI and autoimmune hepatitis, given the absence of pathognomonic features of either condition. However, specific patterns of injury have been described; in particular, significant fibrosis is more

often found in autoimmune hepatitis and unlikely in DILI.¹⁵⁵

Autoimmune-like hepatitis after vaccination against SARS-CoV-2

Several reports have recently described acute liver injury following vaccination against SARS-CoV-2 with clinical, serologic, and histological features suggestive of autoimmune hepatitis, including high IgG concentrations, circulating autoantibodies, and periportal necrosis on liver biopsy.¹⁵⁶⁻¹⁶⁰ The clinical expression of hepatic involvement ranges from mild hepatitis to acute liver failure necessitating liver transplantation.¹⁶¹⁻¹⁶² Vaccines are generally recognized as potential triggers of autoimmune hepatitis.⁹⁴⁻⁹⁷ Immunologic analysis of the liver biopsy of one such patient shows that activated cytotoxic CD8 positive T cells, including spike specific CD8 positive T cells, dominate the intrahepatic infiltrate, possibly indicating the triggering of a CD8 positive T cell driven, immune mediated hepatitis.¹⁶³ A study in 87

patients collected from 18 countries who developed liver injury after SARS-CoV-2 vaccination suggests that the outcome with or without steroid treatment is good in the short term, except for one patient who needed liver transplantation.¹⁶⁴ Among 12 patients in whom steroid therapy was discontinued, no relapse was observed after a median follow-up of four months, whereas three patients with mild liver injury after the first dose developed severe hepatitis following the second dose of the same vaccine.¹⁶⁴ Great caution should be exercised in re-exposing to the same vaccine patients who have experienced liver damage after the first dose. Population based studies and active pharmacovigilance are needed to assess the incidence and clinical relevance of such observations.

Treatment of autoimmune hepatitis

Treating autoimmune hepatitis is complex but rewarding. Untreated autoimmune hepatitis leads to liver failure and death within five years in most

Table 2 | Patient journey in autoimmune hepatitis

Stage	Clinical picture	Decision making and potential mistakes	Patient perspective
Making the diagnosis	Extremely varied; ranges from mild asymptomatic disease to fulminant hepatitis. Any elevation of liver enzymes could be autoimmune hepatitis	Exclusion of other causes (especially viral, Wilson disease, and drug induced). Best screening test total IgG (and IgA, IgM, or γ -globulins), then autoantibodies (ANA, SMA, anti-SLA/LP, anti-LKM1, anti-LC1). Liver biopsy necessary to confirm diagnosis and exclude other causes. Diagnosis often delayed in men, in older people, and in complex patients with additional conditions; comorbidity of fatty liver disease and autoimmune hepatitis becoming more common	Uncertainty during work-up. Dual reaction on diagnosis: on the one hand, relief about definite diagnosis for previously not understood disease; on the other hand, worry about mysterious, poorly understood rare disease. Having to cope with lack of understandable cause (what have I done wrong? In children: what have parents done wrong? Difficult to accept answer that disease is unrelated to behavior, nutrition, stress, or other understandable causes.) Desire for more information and explanations
Induction therapy	All patients experience some degree of steroid side effects; picture may vary a lot: restlessness, sleepless nights, higher fitness, increased hunger, craving for food/sweets, possibly acne and moon face; beware of psychiatric side effects, particularly steroid induced depression, but also manic phases possible	Steroid dosing (usually 0.5 mg/kg body weight prednisolone; more in acute, less in mild disease); adapt steroid dose to individual patient (severity of disease, comorbidity, age; adapt rapidly when side effects occur); do not miss steroid induced hyperglycemia (check repeatedly in first 2 weeks); advice on side effects and diet; when to start azathioprine (usually after 2 weeks; later in marked jaundice). Use elasticity measurement to document regression of liver swelling (inflammation)	Worry about treatment side effects; many questions on prognosis, consequences for personal and professional life; risk for genetically related family members. Risk for infections (recommended vaccines should be given, response monitored; travel advice may be necessary). Necessity to integrate care with possible other medical conditions. Need to develop a therapeutic alliance with treating care team/physician
Maintenance therapy	Treatment guided by laboratory values, not by clinical symptoms, which is difficult to comprehend for patients and doctors alike; side effects may prominently influence therapeutic choices; trustful doctor-patient relationship essential to optimize adherence and to adapt treatment schedule to individual needs and wishes; special challenges in children and adolescents	Treatment aim is full biochemical remission—ie, normal transaminases and IgG; regular (usually every 3 months) laboratory monitoring required; best to measure 6-thioguanine for optimal azathioprine dosing; switch to second line therapy only in definite intolerance. Involve expert center if remission cannot be achieved. Use elasticity measurement to assess fibrosis regression or to detect relapse and progression early. Adherence essential, often challenged by internal (eg, adolescence) and external factors	Worry about long term side effects of immunosuppression (cancer, infections, bone marrow damage). Subjective wellbeing and laboratory findings may not always correlate. Need for open dialog with doctor. Patient empowerment: patient needs to be considered equal partner in doctor-patient relationship. Long term perspectives need to be discussed (prognosis, lifestyle advice; in young patients, pregnancy and professional choices). Search for reliable sources of information; possible help through patients' organizations and expert (reference) centers
Second and third line therapy	Insufficient response despite optimal dosing and adherence to standard therapy; intolerance of azathioprine and 6-mercaptopurine	In intolerance test for 6-mercaptopurine; if that is not tolerated, use MMF. Insufficient response should lead to questioning of diagnosis and of adherence. Third line therapies should be given only in expert centers; pressing need for systematic studies	Frustration and fears, if treatment target is not met. Discuss treatment target with doctor: is complete remission necessary in light of age, comorbidities, side effects? Ask for second opinion in expert center. Information on novel therapies and clinical trials should be offered to patients with suboptimal therapy response
Wishing to stop treatment	Almost every patient wants to stop treatment at some stage of their patient journey	Discuss pros and cons of a trial of treatment cessation with patient repeatedly; define conditions for such a trial and assess individual risk of relapse. Give patient clear advice, but respect patient's decision; otherwise, high risk of non-adherence with insufficient monitoring	The wish to try to stop therapy is natural and should be covered repeatedly in the consultation; however, only 10-20% can successfully be weaned of all immunosuppression: best done after >2 years of full biochemical remission on (low dose) maintenance therapy. Pros and cons need to be discussed openly, and shared decision making should be applied

ANA=antinuclear antibodies; anti-LC1=liver/cytosol antibody type 1; anti-LKM1=liver/kidney microsomal antibody type 1; anti-SLA/LP=soluble liver antigen/liver-pancreas antibodies; MMF=mycophenolate mofetil; SMA=smooth muscle antibodies.

patients, whereas properly treated autoimmune hepatitis has an excellent prognosis with long term survival and a good quality of life. Treatment of autoimmune hepatitis aims to achieve and maintain disease remission leading to symptom resolution and halting or even reversal of liver damage and fibrosis. Treatment should be optimized to reach these aims with a minimum of side effects. Weighing effectiveness against possible side effects requires an individualized approach considering disease related factors such as inflammatory activity and fibrosis stage, as well as patient related factors such as age, comorbidities, and life circumstances, and patients' personal preferences. This particularly applies to children and young adults. To achieve optimal results, individual treatment regimens and compromises between treatment aims and personal choices are needed. Involving a transitional care team is likely to improve adherence, and thus both treatment success and personal wellbeing.

Induction treatment

The first aim of treatment is the induction of a full biochemical response, defined as a normalization of both transaminase and IgG concentrations.¹⁶ A full biochemical response is only a surrogate marker for histological remission, but its predictive power is so high that in most cases transaminase and IgG concentrations are perfectly reliable disease markers. The time needed to achieve remission can differ, and it may often take up to six months. In addition, only about two thirds of patients really achieve full biochemical remission. Mild ongoing disease with transaminase concentrations within two times the upper limit of normal (that is, up to around 80 U/L) was long thought to be acceptable, but observational studies have shown that fibrosis may well progress in such patients.^{29 148} On the other hand, achieving a complete biochemical response not only stops progression of fibrosis but also allows for its regression, leading to an excellent long term prognosis.^{29 148 165} Therefore, achieving a complete biochemical response remains the general aim of treatment.¹⁴

To induce remission, steroids remain the drug of choice, showing very high effectiveness. Response to steroids is universal in autoimmune hepatitis, and non-response to steroids seriously questions the diagnosis or the adherence of the patient to the prescribed treatment. Recommendations vary as to the choice and starting dose of steroid, with limited data for an evidence based recommendation. A recent large retrospective analysis of 451 patients treated at nine centers across Europe showed that a starting dose of 0.5 mg/kg body weight of prednisolone was similarly effective to the widely used and recommended initial 1 mg/kg starting dose, with a slightly slower response rate but fewer side effects.¹⁶⁶ Thus, doses higher than 0.5 mg/kg body weight should be given only in very severe acute disease. In the few cases that manifest as fulminant hepatitis with acute liver failure, higher doses given

intravenously, such as 100 mg prednisolone daily, are used, not only to achieve a faster response but also to enable rapid assessment of response. In acute severe autoimmune hepatitis with liver failure, lack of improvement of liver function within the first seven to 14 days of therapy has been shown to predict a poor prognosis. These are the very few patients with autoimmune hepatitis who may need emergency liver transplantation.^{35 36} Therefore, patients with acute severe autoimmune hepatitis should be transferred promptly to a transplant center, where disease severity and response to treatment can be assessed daily to enable a balanced decision regarding management.

Response to steroids is usually rapid. Transaminase concentrations often start falling within a week, and liver function with lowered bilirubin and international normalized ratio, if impaired, follows promptly. IgG has a longer half-life and therefore falls more slowly. Nevertheless, autoimmune hepatitis is very heterogeneous, not only in its clinical presentation but also in the speed and degree of response to treatment. Consequently, the recent Delphi survey conducted by the International Autoimmune Hepatitis Group had difficulty agreeing on a universal definition of non-response, finally agreeing on a failure to achieve a more than 50% reduction of alanine transaminase concentrations within four weeks.⁶ However, a 50% reduction of alanine transaminase concentrations can usually be achieved within one week, and, depending on disease severity and comorbidities, slower responses should raise questions about diagnosis and treatment schedules.⁶ As soon as a response is observed, the steroid dose should be tapered stepwise, usually in steps of 5 mg every week, down to 10 mg prednisolone per day until a full biochemical response is achieved.

Budesonide has been tested as an alternative to prednisolone or prednisone as a steroid with a high first pass effect in the liver. The large initial randomized trial showed similar effectiveness with fewer side effects in 100 patients receiving fixed dose 9 mg budesonide versus 103 patients in the prednisone arm on a de-escalating schedule.¹⁶⁷ The difference in steroid side effects was entirely due to less acne and moon face, whereas diabetes occurred in four patients in the budesonide arm but in none of the prednisone treated patients. Observational studies and personal experience suggest a slower response rate and thus often a longer time until full biochemical response is achieved.^{168 169} In the medium term, steroid side effects seem to be similarly a problem in budesonide treated patients, who often remain on budesonide for longer than recommended in guidelines. The starting dose of budesonide is 9 mg/day, but tapering can be trickier than with prednisolone owing to the less flexible dose range available on the market.

A very recent large real world study from Spain comparing 105 budesonide treated patients with autoimmune hepatitis and 276 prednisone treated patients confirmed not only a slower response but

also a markedly lower overall response rate, calling into question any advantage of budesonide in autoimmune hepatitis. Furthermore, as the first pass effect of budesonide is dependent on the activity of the metabolizing enzyme cytochrome p450 3A4, and as this enzyme can be suppressed by more than 95% by inflammatory cytokines, budesonide in active autoimmune hepatitis is probably just as much a systemic steroid as prednisone or prednisolone but with a more difficult dosing schedule and less flexibility in dosing. It is therefore not our drug of choice in autoimmune hepatitis. Shortening overall steroid exposure and searching for steroid-free alternatives is on the agenda for the future.^{170 171}

Whereas steroids are the drug of choice for initial response, azathioprine is the drug of choice for maintenance,^{11 12} and it also aids treatment response and helps to reduce steroid side effects. Therefore, azathioprine should be started early, usually after observing an initial steroid response (that is, after seven to 14 days).¹⁷² As about 5% of patients may not tolerate azathioprine, the drug should be started at a low dose, usually 50 mg/day, with monitoring for side effects including full blood counts undertaken every one to two weeks. The dose of azathioprine should then be increased to 1-2 mg/kg body weight. Azathioprine metabolism is altered in severe jaundice, and in these patients initial dosing should be very careful until bilirubin concentrations have fallen to about five times the upper limit of normal.

Maintenance treatment

The art of treating autoimmune hepatitis lies in finding the optimal individual maintenance therapy. For most patients, this is azathioprine 1-2 mg/kg/day as monotherapy or in combination with low dose steroids.^{1 173} If a full biochemical response can be achieved, immunosuppressive therapy should be titrated down to the level needed to retain this full response, and steroids should preferably be tapered out completely, if possible. If disease reactivates during tapering, steroids may need to be reintroduced at a slightly higher dose.

In patients unable to taper steroids completely, as well in all patients not achieving a full biochemical response, azathioprine metabolites should be measured, as azathioprine is a pre-drug and drug metabolism varies considerably.¹⁴ The active metabolite 6-thioguanine should be measured, as well as the alternative inactive metabolite 6-methylmercaptopurine, which is often responsible for drug toxicity. If both 6-thioguanine and 6-methylmercaptopurine are low, the dose should be adjusted. If both are very low, non-adherence should be suspected and corrected, at best with psychological support. If 6-thioguanine is low but 6-methylmercaptopurine is high, drug metabolism can be optimized by adding allopurinol to the regimen while at the same time lowering the azathioprine dose.¹⁴ This regimen can be highly effective but requires both a very cooperative patient and an experienced physician.

Insufficient response and treatment intolerance

Not achieving a full biochemical response—that is, elevated alanine transaminase and/or elevated IgG concentrations—after more than six months of standard therapy is considered an insufficient response.^{6 14} Adverse events possibly related to treatment leading to potential discontinuation of the drug is considered intolerance, which in turn may be a cause for an insufficient response.¹⁴ As an insufficient response is associated with progressive fibrosis and an increased risk of liver failure, strategies to optimize therapy need to be developed (fig 3).¹⁴ This may require a new liver biopsy to assess whether the elevated alanine transaminase concentrations may be due to causes other than continuing autoimmune hepatitis activity such as drug toxicity, comorbid NASH, or other liver diseases. Furthermore, assessing fibrosis stage and inflammatory autoimmune hepatitis activity, best assessed by the histological activity index, is helpful to balance the need for more intensive therapy against possible side effects.

Second line and third line treatments

Intolerance of azathioprine is quite common and usually manifests within the first few weeks of treatment. As the active azathioprine metabolite 6-thioguanine is the optimal drug for treatment of autoimmune hepatitis, before labeling a patient as azathioprine intolerant, an attempt at re-exposure at a low starting dose should be undertaken, preferably with the drug 6-mercaptopurine, the first metabolite of azathioprine, which is tolerated in up to 50% of patients intolerant to the pre-drug azathioprine.^{14 174} If the patient is intolerant of azathioprine and 6-mercaptopurine, the drug of choice as second line therapy is mycophenolate mofetil at a usual dose of 2 g/day. Although mycophenolate mofetil is a very good alternative drug in case of azathioprine intolerance, it is usually ineffective in patients showing an insufficient response to optimized azathioprine therapy.¹⁷⁵ Therefore, when the response is insufficient, 6-thioguanine concentrations should be measured and then the dose of the standard therapy adapted, possibly with the addition of allopurinol. If this fails, third line therapies are indicated.¹⁴ Multiple third line therapies have been described, none of which has been tested in controlled clinical trials. Furthermore, no head-to-head studies have been done. Therefore, application of third line therapy must be considered experimental, and the indication and management should therefore be left to experts in referral centers.

Duration of therapy and trial of drug withdrawal

Considering that autoimmune hepatitis is an idiopathic disease developing on a background of genetic susceptibility, the fact that most patients need long term and usually lifelong therapy is not surprising. In about 10-20% of patients, immunosuppressive therapy can be safely tapered out and the patients remain in remission without

therapy. Success of treatment withdrawal has been shown to be likely only when a complete biochemical response for more than two years on a monotherapy has been achieved, with alanine transaminase concentrations in the lower range of normal and IgG concentrations below 12 g/L.¹⁷⁶⁻¹⁷⁸ In such patients, stepwise complete withdrawal of treatment ought to be attempted, but close follow-up is needed as the relapse rate is high, especially in the first six months after withdrawal. Late relapses can occur, even decades after spontaneous stable remission, so lifelong surveillance is needed in all patients.

Almost all patients want to attempt treatment withdrawal, and proceeding with such an attempt can be justified even in patients who do not fulfill the above positive predictive criteria. For practical purposes, we advocate such an approach under close medical surveillance, as otherwise the risk of non-adherence by the patient is high without close physician-patient cooperation. Once relapse has occurred, both patient and physician are more motivated to pursue long term immunosuppression using the lowest effective dose to keep the disease at bay.

Liver transplantation

The need for liver transplantation in autoimmune hepatitis may be due to acute onset rapidly evolving into severe liver failure or end stage liver disease and its complications, including hepatocellular carcinoma. Over recent decades, listings for liver transplantation for autoimmune hepatitis were substantially stable, between 0.5 and 0.8 per million population per year, in the UK and US, respectively.¹⁷⁹ Survival rates of patients and grafts in European adults from 2000 to 2009 were 88% and 84% at one year and 80% and 72% at five years, respectively.¹⁸⁰ In the US, survival rates of patients and grafts for children transplanted from 2002 to 2012 were 95% and 91% at one year and 91% and 84% at five years, respectively.¹⁸¹ Age significantly affects patients' survival after liver transplantation; in particular, death following infectious complications is more frequent in patients above the age of 50 years.¹⁸² Autoimmune hepatitis recurs in 8-12% of patients within the first year and 36-68% after five years. The diagnostic criteria for recurrent autoimmune hepatitis are the same as for the original disease,⁴ although some features may be less pronounced or absent because of concurrent immunosuppressive therapy or short duration of disease.¹⁸³

Risk of neoplastic disease in autoimmune hepatitis

Hepatocellular carcinoma, a well known complication of liver cirrhosis, is significantly less frequent in patients with autoimmune hepatitis than in those with liver cirrhosis of other causes.¹⁸⁴ Hepatocellular carcinoma develops in 1-9% of patients with autoimmune cirrhosis, with an annual incidence of 1.1-1.9%.¹⁸⁴⁻¹⁸⁶ A recent meta-analysis including 6528 patients with autoimmune hepatitis and a median follow-up of eight years indicates

that the pooled incidence is 3.06 per 1000 patient years in autoimmune hepatitis, but as high as 10.07 per 1000 patient years in patients with cirrhosis at the time of diagnosis of autoimmune hepatitis.¹⁸⁷ Other risk factors are older age, concurrent alcohol consumption, male sex, insufficient control of transaminase, and frequent relapses.^{165 188} Even if recommendations for hepatocellular carcinoma surveillance in autoimmune cirrhosis are not validated, liver ultrasonography every six months may be suggested.¹⁸⁹

In addition to assessing development of hepatocellular carcinoma, assessing the risk of extrahepatic malignancies in chronically immune suppressed patients with autoimmune hepatitis is also clinically relevant.^{74 190 191} Extrahepatic cancers occur in up to 5% of patients with autoimmune hepatitis, non-melanoma skin tumors and hematological cancers being the most common.^{43 191-193} A recent nationwide population based cohort study with more than 5000 patients with autoimmune hepatitis in Sweden quantified the risk of extrahepatic cancer to be 1.3 times higher compared with people without autoimmune hepatitis; beyond 10 years of follow-up the risk remained stable.¹⁹⁴ A Danish nationwide cohort study in a cohort of 1805 patients with autoimmune hepatitis showed a 1.5 times higher 10 year risk of cancer, which increased only slightly with longer duration of immunosuppression.¹⁹⁵

Challenges for non-expert hepatologists

The availability of second line autoantibody serology (that is, confirmatory tests with molecularly expressed antigens) is often limited and its interpretation may be tricky. The correct interpretation of liver histology requires a dedicated and expert pathologist. Tapering and fine tuning of steroid treatment needs personalization on a patient-by-patient basis. Availability of alternative second line immunosuppressive drugs for patients who do not tolerate azathioprine is often limited, and management of non-responding patients requires drugs that are not universally accessible.

Management of the variant syndromes (autoimmune hepatitis-PBC, autoimmune hepatitis-PSC) and autoimmune hepatitis overlapping with NASH/non-alcoholic fatty liver disease requires coordination with additional specialists (radiologist, gastroenterologist, nutritionist). Referral centers for patients with autoimmune hepatitis are not widely diffused. To improve the care of patients with autoimmune hepatitis throughout Europe, the European Reference Network for Hepatological Diseases (ERN RARE-LIVER; <https://rare-liver.eu/>) represents a relevant and practical instrument.

Emerging treatments

The standard therapies for autoimmune hepatitis have remained the same since the 1960s, and progress with novel approaches to therapy has been rather slow for two reasons. Firstly, standard therapy is very

effective and usually well tolerated, thus limiting the need for alternative approaches. Secondly, and probably more importantly, autoimmune hepatitis is a relatively rare and complex disease, making it both less attractive for the pharmaceutical industry and very costly and difficult to do successful controlled clinical trials. In principle, all the new drug therapies for rheumatic diseases and inflammatory bowel diseases might also be effective in autoimmune hepatitis.

Ongoing smaller studies are looking at the use of anti-B cell activating factor in patients with insufficient response,¹⁹⁶ at the use of anti-tumor necrosis factor as alternative steroid-free induction therapy,^{197 198} and at various strategies to increase the number and the activity of regulatory T cells by stimulating the interleukin-2 receptor on regulatory T cells. In view of studies suggesting an inadequate T cell regulatory response in autoimmune hepatitis, these studies look promising. Although standard therapy is very effective in most patients, substantial side effects can occur, treatment needs to be long term, and 20-30% of patients fail to reach a full response. Considering this, an obvious unmet clinical need exists for novel therapies and alternative treatments.¹⁹⁹ Repurposing of immunomodulatory drugs tested in other inflammatory diseases is the most promising avenue, and organizational and funding opportunities for such studies are much needed.

Guidelines

International guidelines on autoimmune hepatitis have been issued in recent years by European, American, and Asian-Pacific liver societies.^{14 200} The main clinical, serologic, and diagnostic topics are similarly covered. The American guidelines have specific sections dedicated to children, to pre-treatment counseling, and to the most sophisticated MRI technologies to assess liver fibrosis. Budesonide is regarded as alternative treatment in the Asian-Pacific guidelines, rather than as first line therapy as suggested by American and European guidelines.

Patient journey in autoimmune hepatitis

Table 2 summarizes the classic journey the typical patient with autoimmune hepatitis has to deal with, according to the personal experience of two patients who we gratefully acknowledge.

Conclusions

Several decades since its original recognition and formal description, autoimmune hepatitis still represents a diagnostic and therapeutic challenge, and its pathogenesis remains largely obscure. Several biochemical, immunologic, and histological features are needed to reach a confident diagnosis of a disease that can attack the liver at any age and with heterogeneous clinical expression. Treatment needs to be tailored individually, taking into account disease severity and stage, comorbidities, and personal characteristics, is usually lifelong, and may

imply a relevant psychological burden. As with other rare diseases, involving expert centers in patient care can improve patients' outcome and help to advance knowledge and clinical care pathways.

GLOSSARY OF ABBREVIATIONS

- Anti-LC1—liver/cytosol antibody type 1
- Anti-LKM1—liver/kidney microsomal antibody type 1
- Anti-SLA/LP—soluble liver antigen/liver-pancreas antibodies
- DILI—drug induced liver injury
- ELISA—enzyme linked immunosorbent assay
- MRI—magnetic resonance imaging
- NASH—non-alcoholic steato-hepatitis
- PBC—primary biliary cholangitis
- PSC—primary sclerosing cholangitis
- SMA—smooth muscle antibodies

QUESTIONS FOR FUTURE RESEARCH

- What are the triggering events and the target antigens for the aberrant autoimmune response in autoimmune hepatitis?
- Can we improve detection and diagnosis of autoimmune hepatitis by simpler and more reliable diagnostic assays, perhaps even making liver biopsy unnecessary?
- Do more effective drug regimens for autoimmune hepatitis exist, minimizing steroid use and side effects?
- How can we improve delivery of care for this complex and variable relatively rare disease combining primary care physicians and expert centers to give the most comfort and security to patients, with optimal treatment results at affordable costs?
- How can aspects related to quality of life be systematically captured as clinical endpoints?

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