

# Epidemiology and treatment of autoimmune hepatitis

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**Abstract:** Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver that occurs worldwide with a low and probably underestimated prevalence. Although it typically affects young and middle-aged women, it can occur in both sexes and across all age groups. AIH runs a fluctuating course, but can present as severe and even fulminant hepatic failure or at a stage of advanced fibrosis or cirrhosis. Prognosis of severe AIH is poor if untreated. The pathogenesis is complex, combining environmental factors (external chemical or infectious triggers) and host genetic susceptibility. The diagnosis is based, after exclusion of other etiologies of chronic liver disease, on a combination of different elements, including the presence of elevated transaminases, elevated immunoglobulin G (IgG) levels, the presence and pattern of typical autoantibodies, and a liver biopsy showing interface hepatitis and other characteristic features. No single test can be used to make the diagnosis. Response to treatment can also help to establish the diagnosis. Simplified criteria can be used to make a bedside diagnosis with relatively high accuracy. Treatment consists of corticosteroids or other immunosuppressive regimens according to the severity of the disease, the response to the treatment, and the tolerance to therapy, with liver transplantation as an ultimate remedy in treatment-resistant cases with liver decompensation.

**Keywords:** autoimmune hepatitis, antibodies, pathophysiology, treatment, epidemiology

## Introduction

Autoimmune liver diseases are the earliest recognized sites of autoimmune diseases<sup>1,2</sup> and are classified in two main entities according to the target cell type of autoimmune injury.<sup>3</sup> In autoimmune hepatitis (AIH), hepatocytes are the target, whereas autoimmune cholangiopathies include disorders of the intrahepatic and extrahepatic biliary system with the cholangiocyte as main target.<sup>4</sup> In some cases both hepatocytes and cholangiocytes are involved, leading to overlap syndromes between AIH and autoimmune cholangiopathies.<sup>5</sup> This review will focus on AIH.

AIH is a chronic and progressive inflammatory disease of the liver, histologically characterized by an interface hepatitis.<sup>3</sup> The disease is further characterized by high but fluctuating levels of aspartate aminotransferase (AST), alanine aminotransferase and IgGs, and by the presence of autoantibodies.<sup>1,6,7</sup> Based on the latter, two types of AIH can be distinguished. Type 1 AIH (AIH-1) is characterized by the presence of antismooth muscle antibodies (ASMA) and/or antinuclear antibodies (ANA), whereas type 2 AIH (AIH-2) typically shows positivity for antiliver/kidney microsome (LKM) type 1 antibodies or antiliver cytosol type 1 antibodies.<sup>3,8</sup> Both types differ in

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age of onset, mode of presentation, geographic distribution, treatment, and successful treatment withdrawal rate.<sup>7</sup>

## Epidemiology and natural history

Data on AIH are rather scarce and suffer from important methodological shortcomings. Most of the data were collected before the introduction of the first International Autoimmune Hepatitis Group scoring system, implying a lack of standardization in diagnosis.<sup>9,10</sup> Furthermore, most of the data were also collected before the discovery of hepatitis C virus (HCV). As patients with HCV are frequently positive for autoantibodies, some patients with HCV might have been misdiagnosed as having AIH.<sup>11</sup> Finally, the diagnosis is often overlooked and in both acute liver failure and the so-called cryptogenic cirrhosis many patients might actually have AIH without being properly diagnosed. For these reasons it is generally accepted that the reported incidences and prevalences are an underestimation of the true values.<sup>7</sup>

Most of the available data are on AIH-1. AIH-1 represents about 80% of AIH cases, occurs worldwide,<sup>3,12,13</sup> and has a strong female predominance: 75% of affected people are female.<sup>14</sup> It was for a long time considered to primarily affect young and middle aged women, with a peak in childhood and another in adulthood around the age of 40.<sup>3</sup> It has, however, become clear that elderly people can also be affected and that the disease can have its first manifestation even at an advanced age: 20% of patients present after the age of 60 years.<sup>15</sup> In Norway the annual incidence was reported to be 1.9 cases per 100,000 with a prevalence of 17 cases per 100,000.<sup>16</sup> In the US an annual incidence of 1 per 200,000 cases was reported.<sup>6</sup> A Spanish report shows similar findings, with an annual incidence of 0.8 cases per 100,000 and a prevalence of 11.6 cases per 100,000<sup>17</sup> leading to an estimated point prevalence of 10 to 15 cases per 100,000.<sup>4</sup> The clinical presentation can be variable.<sup>6,15,18</sup> An incidental finding of elevated transaminases during a routine investigation may lead to its diagnosis. Nonspecific symptoms such as fatigue and arthralgia are often present. It can also present as an acute hepatitis or even as fulminant liver failure.<sup>15</sup> Recently an increase in the number of patients presenting with acute hepatitis has been reported in Japan.<sup>19,20</sup> AIH often has a chronic and fluctuating course, and about 30% of patients already have cirrhosis at the time of diagnosis, indicative of a longstanding process.<sup>21</sup> Complications of cirrhosis may occasionally be the mode of presentation. Children and young adults often present with a more acute onset than elderly patients.<sup>22</sup>

The course of AIH is therefore not always benign. Patients presenting with untreated severe disease are at high risk of death: 40% die within 6 months of diagnosis.<sup>23</sup> Those who survive develop cirrhosis in >40% of cases.<sup>24</sup> Patients with cirrhosis develop esophageal varices within 2 years in 54% of cases,<sup>25</sup> of whom 20% will eventually die of hemorrhage.<sup>26</sup> Sustained elevation of transaminases >10 × upper limit of normal (ULN) or a combination of transaminases >5 × ULN and gammaglobulins >2 × ULN are predictors of early mortality.<sup>27</sup> AIH accounts for 2.6% of the liver transplantations in Europe and 5.9% in the US.<sup>28,29</sup> Adequate treatment markedly improves prognosis<sup>23,25</sup> with 10-year survival rates reaching 98%.<sup>30,31</sup> The absence of normalization of transaminases while on treatment is associated with a poorer prognosis, including a higher risk of developing hepatocellular carcinoma.<sup>30,31</sup>

AIH-2 is thought to be less frequent, although it is probably underdiagnosed and underreported.<sup>22</sup> It mainly affects children and young adults and presents more frequently as fulminant hepatic failure.<sup>32</sup>

Autoimmune liver diseases and AIH can present as a single-organ autoimmune disorder, but associated autoimmune disease of other organs can be observed and AIH can also present in the context of a systemic autoimmune disease.<sup>3,33</sup> Autoimmune thyroiditis is most frequently encountered. Genetic predisposition might influence the susceptibility for concurrent extrahepatic disease.<sup>34</sup>

## Etiopathogenesis of AIH

AIH is a complex disease, in which environmental factors (external chemical or infectious triggers) and the host's genetic susceptibility coinduce the loss of self-tolerance and subsequently the development of the disease.

Drug exposure is frequently present in AIH. Reactive metabolites created through hepatic metabolism of some drugs have been shown to bind to cellular proteins such as cytochrome P450. These can then be recognized by the immune system as neoantigens. Drug-induced AIH has been well documented for nitrofurantoin and minocycline, prompting a pattern of AIH not requiring long-term immunosuppressive therapy.<sup>35,36</sup> Recently, antitumor necrosis factor (TNF)- $\alpha$  agents have been described as responsible for drug induced-AIH with favorable prognosis.<sup>37</sup> Moreover, the risk of recurrent drug induced liver injury (DILI) due to drugs such as cholesterol-lowering agents, TNF- $\alpha$  antagonists or antibiotics (such as fluoroquinolones) has to be considered. These drugs or their metabolites may share sufficient similarity to provide immunological cross-sensitization or they may share

a common target leading to DILI as a consequence of the drug actions. In these cases the probability of making a diagnosis of AIH-DILI increases in the second episode.<sup>38</sup>

Genetic predisposition is a prerequisite of AIH. The genes associated with AIH do not follow a Mendelian mode of inheritance; conversely, they operate as “complex trait conditions”, in which one or more genes act to increase or reduce the risk of the trait interacting with environmental factors.

The genes most strictly involved in AIH are located on the short arm of chromosome 6, within the human leukocyte antigen (HLA) class II region, with particular regard to the ones encoding allelic variants of DRB1.<sup>39</sup> AIH-1 susceptibility has been associated with DRB1\*0301 and DRB1\*0401<sup>40,41</sup> in white North American and Northern European individuals and to DRB1\*0405 and DRB1\*0404 in Japan, Argentina, and Mexico.<sup>42</sup> In a Japanese population, DRB1\*02 appears to be associated with a lower rate of concurrent autoimmune disease, whereas DRB1\*04 is associated with higher IgG levels.<sup>34</sup> Moreover, in South American children, DRB1\*1301 has been associated with an early-onset severe disease.<sup>43</sup> Conversely, AIH-2 susceptibility is related to DRB1\*0701 and to DRB1\*0301, the former having a worse outcome.<sup>44</sup> Interestingly, AIH can be present in 10% of patients affected by autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, also known as autoimmune polyendocrine syndrome type 1, which is caused by homozygous mutations in the AIRE1 gene, a transcription factor involved in clonal deletion of self reactive T cells.<sup>45</sup> Additional possible susceptibility genes include TNF- $\alpha$  and - $\beta$ , major histocompatibility complex-encoded complement, the major histocompatibility complex class I chain-related A and B,<sup>46</sup> cytotoxic T lymphocyte-associated antigen (CTLA) 4,<sup>47</sup> interleukin-2 (IL-2), IL-4 and IL-6,<sup>48</sup> and vitamin D receptor<sup>49</sup> genes.

Within these permissive genetic profiles infectious agents could have a possible role in the process of disease development. It has been hypothesized that the initiation of autoimmune damage is due to “molecular mimicry”, that is, to an immune response directed to a self-antigen structurally similar to external pathogens. In particular, shared homology can be identified between the cytochrome mono-oxygenase CYP2D6 and some viral epitopes, hence LKM-1 autoantibodies cross-react with homologous regions of CYP2D6, HCV, herpes simplex virus, and cytomegalovirus. According to this model the exposure to these pathogens may prime a cross-reactive subset of T cells in a genetically permissive background.<sup>50,51</sup> Moreover, it has been reported that

DRB1\*1301 is associated with persistent hepatitis A virus infection,<sup>43</sup> which highlights a possible role of hepatitis A virus in the pathogenesis of AIH. Viral infections could also act as nonspecific triggers leading to nonspecific activation and proliferation of resting T cells, as reported in Epstein–Barr virus infection, or to the release of sequestered antigens from hepatocytes within a proinflammatory environment.<sup>52</sup> Moreover, among the bacterial agents, *Coxiella burnetii* could trigger an autoimmune liver disease.<sup>53</sup>

The autoantigens associated with AIH are various. AIH-2 is a particular “disease model” since its autoantigen has been identified in the above-mentioned CYP2D6, which is the target of anti-LKM-1 autoantibodies. These autoantibodies recognize linear regions of CYP2D6 in a hierarchical manner, namely CYP2D6<sub>193–212</sub> in 93%, CYP2D6<sub>257–269</sub> in 85%, CYP2D6<sub>321–351</sub> in 53%, CYP2D6<sub>410–429</sub> in 13%, and CYP2D6<sub>373–389</sub> in 7% of cases.<sup>54</sup> However, many other substrates can be encountered. The transfer ribonucleoprotein complex tRNP(Ser)Sec is bound by antisoluble liver antigen (SLA), 80 formiminotransferase cyclodeaminase is recognized by anti-liver cytosol type 1 and uridine triphosphate glucuronosyltransferase is recognized by anti-LKM-3.<sup>55</sup> Moreover, antibodies to liver microsomes primarily bind to cytochrome CYP1A2 and are associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.<sup>56</sup> Interestingly, these autoantibodies were first described in patients with AIH induced by dihydralazine.<sup>57</sup>

Various mechanisms underlie the autoimmune liver attack. Liver infiltrates in AIH reveal a predominant presence of CD4<sup>+</sup> helper/inducer cells but also, albeit to a lesser extent, the presence of CD8<sup>+</sup> cytotoxic/suppressor cells, natural killer (NK) cells, monocytes/macrophages and B lymphocytes.<sup>58</sup> A key role in liver damage is attributed to autoreactive CD4<sup>+</sup> T lymphocytes that become activated after the presentation of a self antigenic peptide embraced by an HLA class II molecule by antigen-presenting cells and the interaction between receptors and coreceptors, such as CD28 expressed by CD4<sup>+</sup> Th0 cells and CD80 expressed by antigen-presenting cells. The subsequent differentiation of the Th0 cells is influenced by the cytokine environment. IL-12 delivered by macrophages favors the differentiation into Th1, which in turn releases IL-2 and interferon- $\gamma$ , that promote macrophage activation, stimulate CTLs, enhance the expression of HLA class I and induce the expression of HLA class II on hepatocytes (that is normally not present). Conversely, IL-4, IL-10, and IL-13 foster the production of antibodies by B lymphocytes.<sup>7</sup> These immunoglobulin G (IgG) coat the hepatocyte surface in AIH and render these

cells susceptible to cytotoxic attacks by Fc-receptor-bearing cells, including NK. NK, besides inducing apoptosis, can also have an anti-inflammatory and immune suppressive role producing cytokines such as IL-4 and regulating the differentiation of T regulatory (T reg) cells.<sup>59</sup> Growing evidence has highlighted the role of immunoregulatory mechanisms, and in particular of their impairment, in AIH. Organ-specific autoimmunity is driven by the interplay between T effector and antigen-specific inducible T reg that determine the duration, extent, and distribution of inflammation within the organ.<sup>60</sup> T reg cells derive from CD4<sup>+</sup> Th0 cells in the presence of transforming growth factor- $\beta$  and constitutively express the CD25 (IL-2 receptor- $\alpha$  chain). In addition, they express CD62L (glucocorticoid-induced TNF receptor), CTLA4 and FOXP3 (forkhead/winged helix transcription factor), the latter being crucial for their function.<sup>61</sup> They prevent the proliferation of autoreactive cells, suppressing effector T cell immune responses. In AIH the number and function of T regs are impaired, especially at diagnosis and at relapse during drug-induced remission.<sup>62,63</sup> Moreover, in children with AIH-2, the quantities of T reg inversely correlate with disease severity as well as with titers of anti-SLA and anti-LKM-1 autoantibodies.<sup>61</sup> In the presence of TGF- $\beta$  and IL-6, Th0 differentiate into IL-17-producing T cells (Th17). This subset of cells has been recently described in human autoimmune liver diseases and AIH.<sup>64,65</sup> IL-17 appeared to be significantly upregulated in animal models of AIH<sup>66</sup> and human AIH.<sup>66,67</sup> It has been reported that there are increased levels of IL-17 in the peripheral blood of AIH patients and an expanded Th17 cell population both peripherally and within the liver, the latter data being positively correlated with the degree of inflammation and the stage of fibrosis.<sup>67</sup> Moreover, IL-17 stimulates IL-6 expression, which favors Th17 proliferation while reducing the development of T reg cells. Therefore, IL-17 may orientate the balance between Th17 and T reg cells towards Th17, which is critical for the development of autoimmune diseases.<sup>67</sup>

## Diagnosis

AIH should be considered in the differential diagnosis of patients with elevated liver enzymes and/or unexplained cirrhosis at any age. The diagnosis can be challenging given the absence of a single diagnostic marker and the variable clinical and laboratory findings. AIH is characterized by interface hepatitis, absence of other causes for the lesions eg, viral hepatitis or drug-induced hepatitis, and signs of autoimmunity (autoimmune antibodies or concomitant autoimmune diseases).<sup>68</sup>

## Autoantibodies

As outlined above, AIH results from loss of tolerance of immunocompetent cells to autologous hepatic tissue components and thus constitutes a pathogenetically inhomogeneous entity.<sup>69</sup> The presence and pattern of autoantibodies are important elements in establishing the diagnosis, in making the differential diagnosis with other immune-mediated hepatobiliary diseases, and in identifying the type 1 or 2 variant.<sup>3</sup> We briefly discuss the most important autoantibodies.

Anti nuclear antibodies (ANA) can be considered as a generic term referring to antibodies with specificity for antigens in the cell nucleus. Antigens in the nucleus are present on nucleic acid molecules (RNA and DNA), or protein histones and nonhistones, and on determinants consisting of both nucleic acid and protein molecules (eg, the ribonucleoprotein antigen, antigen U-RNP). Different ANA have specificity for these different nuclear components. ANA are usually directed against double stranded DNA as in systemic lupus erythematosus but the target epitope appears to be different in both diseases.<sup>70</sup> ANA can be detected in patients serum using the conventional method by immunofluorescence or by the more recent enzyme-linked immunosorbent assay technique. They are typically positive in AIH-1.

Antismooth muscle antibodies (ASMA) show specificity for actin and other cytoskeleton components and are frequently present in AIH-1.<sup>71,72</sup> Positivity for ASMA is, however, also seen in primary sclerosing cholangitis.

Anti-LKM-1, LKM-2, and LKM-3 and the liver microsomal type antibodies are microsomal auto-antibodies in AIH-2. As stated above, these antibodies are directed against the cytochrome 50 KD P450 db1 (CYP2D6) microsomal antigen and the 50 KD P450 2A2 antigen, respectively.<sup>73,74</sup> Their staining pattern in the immunofluorescence assay is similar to those of antimitochondrial antibodies.

SLA antibodies are directed against cytosolic liver proteins identified as cytokeratins 8 and 18 which are also present in several other tissues.<sup>75,76</sup> A more specific autoantibody against a cytosolic epitope is Anti-LC-1 (antibodies against liver-specific cytosol antigen type 1).

Liver membrane antibodies combine a set of antibodies against membrane lipoproteins, some of which are liver specific. One of the specific liver specific antibodies is anti-ASGP-R, which reacts with galactose residues of asialoglycoprotein receptor.

Perinuclear antineutrophil cytoplasmic antibodies are heterogenous auto-antibodies present in some patients with AIH.<sup>3</sup>

Antimitochondrial antibodies are usually absent in AIH. If they are present, the diagnosis of primary biliary cirrhosis or an overlap syndrome should be considered.

Autoantibodies are not only useful in the diagnosis of AIH but might also have prognostic implications. SLA antibodies are particularly useful, as they are associated with a higher frequency of liver failure, severe histological alterations, long duration of treatment, and a high relapse rate after drug withdrawal.<sup>77</sup>

## Pathology

Liver biopsy remains essential in the diagnosis of AIH both to establish the diagnosis and to assess disease severity.<sup>3</sup> No histological findings are, however, pathognomonic. The most typical feature is interface hepatitis, which is found in the presence of an inflammatory infiltrate located at the membrana limitans of the portal area and extending into the surrounding liver parenchyma.<sup>11,18</sup> Interface hepatitis can, however, also be present in other liver diseases, especially viral hepatitis. The infiltrate is typically lymphoplasmocytic. Plasma cells are abundantly present both at the portoparenchymal interface and in the liver lobules in typical cases, but lower numbers do not exclude a diagnosis of AIH.<sup>7</sup> Pyknotic necrosis and hepatocyte swelling are other typical but not pathognomonic features. The pathology can be severe, with extensive panlobular hepatitis. In fulminant cases, extensive necrosis and collapse can be seen. In a recent series zone 3 necrosis was a typical feature of patients presenting with acute hepatitis.<sup>20</sup> Advanced fibrosis or cirrhosis is frequently present, even in acute cases, illustrating the often longstanding chronic course of the disease. Patients presenting with bridging necrosis or multi-acinar necrosis progress to cirrhosis in 82% of cases within 5 years and have a mortality rate of 45%.<sup>26</sup>

Liver biopsy can also show features of biliary damage pointing towards autoimmune cholangiopathy or overlap syndromes<sup>78</sup> and can also show features suggestive of other liver diseases.<sup>8</sup> The differential diagnosis with other liver diseases, especially with viral hepatitis and with DILI might be difficult, especially in less typical cases.<sup>79</sup>

The heterogeneity of the clinical picture and the relative rarity of the disease often make the diagnosis difficult, especially in nonspecialist units. In 1993, the International Autoimmune Hepatitis Group (IAIHG), proposed a set of descriptive diagnostic criteria that were recommended in routine clinical practice to classify patients as having “definite” or “probable” AIH.<sup>9</sup> Female gender, elevation of the parenchymal liver enzymes AST or alanine

aminotransferase, autoantibodies, negative viral markers, absence of hepatotoxic drugs or alcohol use, and autoimmune disease in patient or first-degree relatives, are considered typical for AIH. Features considered typical for AIH result in the addition of points, whereas features implicating other liver diseases result in a points decrease. Optional parameters are histological features and response to therapy. This scoring system was developed as a research tool. Czaja and Carpenter validated these criteria in 119 AIH patients.<sup>80</sup> The sensitivity for a definite diagnosis was 82% and specificity was 98%. The specificity for patients scoring a probable diagnosis was only 66%.

## Scoring systems

In 1999 the IAIHG revised the criteria to reduce the likelihood of a probable diagnosis especially in patients with biliary tract disease.<sup>10</sup> In this revised scoring system, the treatment response is graded and a score can be considered before and after treatment. A pretreatment score of ten points or higher, or a posttreatment score of twelve points or higher indicate probable AIH. A pretreatment score of ten points has a sensitivity of 100%, specificity of 73%, and diagnostic accuracy of 67%. A pretreatment score of 15 points, indicative of “definite AIH” has a sensitivity of 95%, specificity of 97%, and diagnostic accuracy of 94%.<sup>33</sup>

As the original scoring system and its revision are too complex for everyday use, the IAIHG developed a simplified scoring system, based on only four independent variables: presence and level of autoantibody expression by indirect immunofluorescence, serum IgG concentration, compatible or typical histological features, and the absence of viral markers.<sup>81</sup> This simplified score is presented in Table 1. The new simplified score was specifically designed to help at the bedside and not primarily for scientific studies. In addition, it was meant to also be applicable in countries with a high viral hepatitis rate. Its clinical usefulness and scientific validity has been assessed by many groups and has been found to be reliable in highly heterogeneous populations in different regions in the world.<sup>33,82–85</sup> The median overall sensitivity for probable AIH ( $\geq 6$  points) was 91% and specificity 94%. For those classified as definite AIH ( $\geq 7$  points) the median overall sensitivity was 75.5% and specificity 100%.<sup>33,82,83</sup> Almost all these studies have a methodological problem (what is the gold standard?), as the included patients were based on the 1999 scoring system. Response to immunosuppressive therapy is such a characteristic hallmark of AIH that this criterion should be included in the final analysis of patients correctly classified as AIH; duration of inflammation

**Table 1** Simplified diagnostic criteria for autoimmune hepatitis

Variable	Cut-off	Points	Cut-off	Points
ANA or SMA	≥ 1/40	1	≥ 1/80	2
LKM			≥ 1/40	
SLA			Positive	
IgG	ULN	1	> 1.1 × ULN	2
Histology	Compatible with AIH*	1	Typical of AIH*	2
Absence of viral hepatitis			Yes	2

**Notes:** Copyright © 2008, John Wiley & Sons. Modified with permission from Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169–176. Probable AIH: ≥6 points; definite AIH: ≥7 points; maximum number of points for all autoantibodies is 2; total is 8 points.

\*Histology

- Compatible with AIH: chronic hepatitis with lymphocytic infiltration without features considered typical.
- Typical of AIH:
  1. Interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending in the lobule.
  2. Emperipolesis (active penetration by one cell into and through larger cell).
  3. Hepatic rosette formation.
- Atypical: showing signs of another diagnosis like NAFLD.

**Abbreviations:** AIH, autoimmune hepatitis; ANA, antinuclear antibodies; IgG, immunoglobulin G; LKM, liver/kidney membrane microsome; NAFLD, nonalcoholic fatty liver disease; SLA, soluble liver antigen; SMA, smooth muscle antibodies; ULN, upper limit of normal.

more than 6 months should be documented to distinguish from drug-induced immune mediated hepatitis.

## Management of AIH

### Indications for treatment

As outlined above, severe untreated AIH has a poor prognosis.<sup>23</sup> Prognosis can be markedly improved by adequate treatment. Based on the factors associated with a poor prognosis, absolute indications for treatment of AIH have been established. A few randomized, controlled trials have demonstrated that patients with AST levels of at least 10 × ULN or more than fivefold ULN in conjunction with a serum gammaglobulin level more than twofold ULN have a high mortality if untreated.<sup>23,25,86,87</sup> The last placebo-controlled immunosuppressive trial containing an untreated arm was published in 1980.<sup>87</sup> The value of these studies is limited as the patients were not characterized by standard diagnostic criteria. Nevertheless these studies revealed that untreated patients have a very poor prognosis with 5- and 10-year survival rates of 50% and 10%, respectively. Histologic findings of bridging necrosis or multilobular necrosis at presentation progress to cirrhosis in 82% of untreated patients and are associated with a 5-year mortality of 45%.<sup>26,88,89</sup> Incapacitating symptoms, associated with hepatic inflammation such as fatigue and arthralgia, are also indications for treatment.<sup>90</sup>

Symptomatic patients with serum AST and/or gammaglobulin levels less than the absolute criteria and with interface hepatitis, may also be indicated for immunosuppressive treatment on an individualized basis, balanced against the possible risk of therapy. Patients with minimal or no disease should not be treated but followed closely.

Immunosuppressive treatment should not be instituted in patients with serious pre-existing comorbidities (vertebral compression, psychosis, brittle diabetes, or uncontrolled hypertension), or previously known intolerance to steroids. Azathioprine should not be started in patients with severe pretreatment cytopenia (leukocyte <2.5 × 10<sup>9</sup>/L or platelets <50 × 10<sup>9</sup>/L) or known deficiency of thiopurine methyltransferase activity.<sup>90</sup> The present review will be limited to a discussion of the treatment regimens in adults.

## Standard treatment

The standard treatment for AIH is based on the results of randomized trials in the 1970s, showing a survival benefit of corticosteroid treatment.<sup>23,25,86</sup> These trials also demonstrated the dismal prognosis of untreated symptomatic AIH, with 5-year survival below 25% in untreated patients versus 80% in those treated with corticosteroids.<sup>87</sup>

The American Association for the Study of Liver Diseases practice guidelines<sup>90</sup> recommends either monotherapy with prednisone at a starting dose of 40–60 mg daily, or a lower dose of prednisone (30 mg daily) combined with azathioprine (1–2 mg/kg body weight), based on the Mayo Clinic trial,<sup>23</sup> and can be considered evidence-based. Prednisone may be reduced by 10 mg per week to a maintenance dose of 20 mg. Further reductions can be considered to 10, 5, or 2.5 mg daily. The use of the prednisone metabolite prednisolone, used more frequently in Europe, is equally effective as chronic liver disease does not seem to have an effect on its synthesis.<sup>26</sup> A higher starting dose (1 mg/kg body weight) of prednisolone might induce remission more quickly and helps to spare steroids in long term.<sup>91</sup>

Steroid-related side effects include acne, facial rounding, striae, weight gain, hirsutism, and emotional instability. Serious complications including steroid diabetes, osteopenia, aseptic bone necrosis, psychiatric symptoms, hypertension, and cataract formation should be anticipated in long-term treatment. Side effects are present in 80% of patients after 24 months of treatment. Azathioprine-related side effects include bone marrow suppression, nausea, vomiting, rash, cholestatic hepatitis, and pancreatitis. Cytopenia is not predictable by testing for thiopurine methyltransferase activity. Determination of this enzyme activity is only warranted when

there is pretreatment or intratreatment cytopenia, or need for higher than conventional doses.<sup>92</sup> The overall frequency of azathioprine-related side effects in patients with AIH is 10% at a dose of 50 mg daily.<sup>93</sup>

Outcomes of standard therapy can be classified as remission, relapse, and treatment failure. Complete remission is characterized by the disappearance of clinical symptoms and complete normalization of all inflammatory parameters including histology. It can be achieved in 65%–75% of patients after 24 months of treatment. As the histological resolution of inflammation lags behind the biochemical response by 3 to 6 months, therapy has to be continued beyond the normalization of aminotransferase levels. At least 3 years of continuous therapy is recommended.<sup>90</sup> Tapering regimens aiming at withdrawal should be attempted with great caution and only after obtaining a liver biopsy demonstrating a complete resolution of inflammatory activity. In that case prednisolone can be tapered over the course of 4–6 weeks to test whether a sustained remission has been achieved. While steroids are the drug of choice for induction of remission, azathioprine is the drug of choice for maintenance of remission.<sup>94</sup> Remission can be sustained by azathioprine monotherapy of 2 mg/kg daily.<sup>95</sup>

Relapse is characterized by increase of aminotransferase levels and reoccurrence of clinical symptoms either under treatment, following tapering of steroids, or after complete withdrawal of therapy. It is present in 50% of patients within 6 months of treatment withdrawal and 80% after 3 years. Occurrence of a relapse requires reinitiation of standard therapy until remission. Therapy can then be tapered to monotherapy with azathioprine 2 mg/kg daily or low-dose prednisolone in patients intolerant to azathioprine. Attempts at withdrawal in all patients with longstanding ( $\geq 12$  months) inactive disease can be considered.<sup>96</sup>

Treatment failure, characterized by progression of the disease during standard therapy, is seen in about 10% of patients. In these cases the diagnosis of AIH should be carefully reconsidered. Experimental regimens can be administered.

## Alternative treatments

Budesonide is a synthetic steroid with high first-pass metabolism in the liver of almost 90%, in principle capable of limiting systemic side effects compared with conventional steroids. Compared with prednisone, the absolute bioavailability is less than sixfold lower.<sup>97</sup> In a large European study a combination of budesonide and azathioprine was evaluated in noncirrhotic patients.<sup>98</sup> Budesonide at a dose of 3 mg three times daily (tapered to bid upon biochemical remission

after 2 weeks, depending on clinical judgment) was compared with prednisone 40 mg daily (reduced per protocol) (both arms plus azathioprine 1–2 mg/kg daily). At 6 months, remission was achieved in 60% of the budesonide group but in only 39% of the prednisone group. In the budesonide group a substantial superior profile of steroid-related side effects was noted. It should be noted that the remission rate in the prednisone group is much worse than reported with a higher starting dose of prednisone and tapered according to biochemical response.<sup>91</sup> In addition, budesonide was not tested in cirrhosis because of possible shunting. However, the trial shows that budesonide can be considered a valid alternative in patients at risk of adverse effects from steroids.

In patients who are intolerant to azathioprine, mycophenolate mofetil (MMF) seems to be a relatively good alternative.<sup>99–101</sup> In another study of patients with AIH experiencing azathioprine failure or intolerance, however, there was no significant benefit with MMF.<sup>102</sup> There are, however, no controlled clinical trials evaluating MMF in treatment naïve or treatment experienced patients with AIH. In a recent prospective study, MMF in combination with prednisolone was evaluated as an alternative to azathioprine in the first-line treatment of AIH. Biochemical response rates were excellent with 88% of the 59 patients achieving complete remission within the first year of treatment.<sup>103</sup> Using MMF as first line treatment of patients with AIH has several drawbacks such as costs (about 15 times higher than azathioprine) and teratogenicity.<sup>104</sup>

Calcineurin inhibitors (cyclosporine A, tacrolimus) have also been used.<sup>105–107</sup> The principal difficulty in advocating for these drugs in first-line therapy relates to their toxicity profile particularly with long-term use. Furthermore, these drugs are not immunomodulatory and therefore require permanent treatment.

Liver transplantation is the treatment of choice in case of fulminant hepatic failure and those who progress to end-stage liver disease despite immunosuppression.

## Conclusion

AIH is a chronic inflammatory disease of the liver occurring worldwide in both sexes and across all age groups. The pathogenesis is complex, combining environmental and genetic factors. The diagnosis is based on a combination of elevated transaminases, the presence and pattern of typical autoantibodies, and a liver biopsy showing interface hepatitis and other typical features. Response to treatment can also help to establish the diagnosis. Simplified criteria can be used to make a bedside diagnosis with relatively high accuracy. Treatment consists of corticosteroids or other

immunosuppressive regimens according to the severity of the disease, the response to treatment, and the tolerance to therapy.

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## Disclosures

The authors report no conflicts of interest in this work.

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