Waldenström first described the disease entity now termed autoimmune hepatitis (AIH) in 1950, when he observed a chronic form of hepatitis in young women. This hepatitis led to cirrhosis and was associated with jaundice, elevated gamma globulins, and amenorrhea. The disease was found to be associated with other autoimmune syndromes and was later termed "lupoid hepatitis" because of the presence of antinuclear antibodies (ANA); however, the term "lupoid" hepatitis has been abandoned because AIH is not part of the organ manifestations of systemic lupus erythematosus.

The identification and characterization of serum autoantibodies have been a driving force in the systematic evaluation, classification, and diagnosis of AIH. Beginning in the 1970s, the detection of autoantibodies against proteins of the endoplasmic reticulum (microsomes) expressed in liver and kidney (liver-kidney microsomal antibodies, LKM) led to the identification of a second form of AIH not characterized by ANA. Molecular analysis soon identified cytochrome P450 (CYP) monoxygenases as hepatocellular target antigens of LKM-1 autoantibodies found in this second form of AIH (AIH type 2). Finally, a third serologically defined group of AIH was categorized after the detection by radioimmunooassay of antibodies to a soluble liver antigen (SLA) identified in the 100,000 g supernatant of liver homogenates. It is evident from the chronology of events that AIH does not represent a homogeneous entity and that seroimmunologic and genetic markers discriminate among its subgroups. AIH is a chronic, mainly periportal hepatitis associated with hypergammaglobulinemia and circulating autoantibodies, which, in most cases, responds to immunosuppressive treatment. There is a striking prevalence among females, an immunogenetic association with the HLA A1-B8-DR3 or DR4 haplotype, and the presence of extrahepatic syndromes. This complex definition indicates that a single cause or a single test for the accurate diagnosis of AIH has not been found. In contrast, the diagnosis is established by a number of diagnostic criteria, as recently defined by the International Autoimmune Hepatitis Group (IAHG), and the exclusion of other causes of chronic hepatitis (Tables 1 and 2). However, AIH frequently overlaps with other autoimmune liver diseases that affect the biliary tract: primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

The combination of seroimmunologic and molecular biologic tests with a recently revised diagnostic scoring system permits a precise discrimination between AIH and other causes of chronic hepatitis. The exclusion of replicating hepatitis virus infection together with female sex, hypergammaglobulinemia, and response to immunosuppressive treatment are the hallmarks of an accurate diagnosis.

**Definition of AIH**

As long as the trigger/cause of AIH is not known, the determination is required whether AIH represents an etiologically heterogeneous syndrome or a single disease entity with a clinically differing rate of progression. Attempts to subclassify AIH have been based on the serologic autoantibody profile or on genetic markers. The diagnosis of AIH cannot be based on characteristic histologic markers; however, the histologic assessment of liver tissue is required for grading and staging as well as for therapeutic monitoring. The exclusion of viral hepatitis is achieved by the use of reliable, commercially available tests and should minimally include hepatitis A, B, and C viruses. Exclusion of hepatitis E virus infection cannot be generally recommended. In addition, the exclusion of other hepatotropic viral pathogens (i.e., cytomegalovirus, Epstein–Barr virus, other herpes group

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**Abbreviations used in this paper:** AIH, autoimmune hepatitis; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic autoantibodies; APS-1, autoimmune polyendocrine syndrome type 1; ELISA, enzyme-linked immunosorbent assay; HCV, hepatitis C virus; HDV, hepatitis D virus; IAHG, International Autoimmune Hepatitis Group; LC-1, liver cytosolic antigen 1; LKM, liver-kidney microsomal antibodies; LP, liver-pancreas antigen; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibodies; tRNA, transfer RNA.

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viruses) is only recommended in cases suspicious of such infections but may be helpful if the diagnosis of AIH based on the above criteria is unclear. Antibody testing should include immunofluorescence testing for antimitochondrial antibodies (AMA).\textsuperscript{23} If these are positive, testing for reactivity with the PBC-associated autoantigens E2 subunit of pyruvate dehydrogenase and E2 subunit of branched-chain ketoacid dehydrogenase may be helpful to exclude PBC or to document an overlap syndrome. If a cholestatic biochemical profile (alkaline phosphatase elevation) is present, cholangiography is required to exclude PSC or overlap of PSC and AIH, which is more frequent in children.\textsuperscript{20} Noninvasive magnetic resonance cholangiopancreatography is under evaluation as a substitute for the more invasive endoscopic retrograde cholangiopancreatography. The following standard tests to exclude the major genetic causes of chronic liver disease may be necessary to complete the diagnostic evaluation: Wilson’s disease, hemochromatosis, and α\textsubscript{1}-antitrypsin deficiency.

**Table 1. The Diagnosis of AIH Is a Diagnosis of Exclusion**

<table>
<thead>
<tr>
<th>Suspected differential diagnosis</th>
<th>Test performed to exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C infection (HCV)</td>
<td>Anti HCV (HCV RNA)</td>
</tr>
<tr>
<td>Hepatitis B and D (HBV, HDV)</td>
<td>HBsAg, anti-HBc (HBV DNA)</td>
</tr>
<tr>
<td>Hepatitis A virus (HAV)</td>
<td>Antibodies, serology: IgG, IgM</td>
</tr>
<tr>
<td>Hepatitis E virus (HEV)</td>
<td>Only if suspected</td>
</tr>
<tr>
<td>EBstein–Barr virus (EBV)</td>
<td>Only if suspected</td>
</tr>
<tr>
<td>Herpes simplex virus (HSV)</td>
<td>Only if suspected</td>
</tr>
<tr>
<td>Cytomegalovirus virus (CMV)</td>
<td>Only if suspected</td>
</tr>
<tr>
<td>Varicella zoster virus (VZV)</td>
<td>Only if suspected</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
<td>History, if applicable withdrawal of drug</td>
</tr>
<tr>
<td>Primary biliary cirrhosis (PBC)</td>
<td>Antimitochondrial antibodies (AMA)</td>
</tr>
<tr>
<td>Liver histology: copper deposition in bile ducts Unresponsive to steroids</td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>Cholangiography</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Ceruloplasmin, urine copper, eye examination, quantitative copper in liver biopsy</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Serum ferritin, serum iron, transferrin saturation, liver histology: iron staining, quantitative iron in biopsy Genetic testing: C282Y, H63D mutation of HFE gene in Caucasoids</td>
</tr>
<tr>
<td>α\textsubscript{1}-Antitrypsin deficiency</td>
<td>Phenotype testing: PiZZ/PiSS/PiMZ/PiSZ</td>
</tr>
</tbody>
</table>

**Diagnostic Score of AIH**

The diagnosis of AIH is established with the aid of a revised scoring system devised by the IAHG and the International Association for the Study of the Liver.\textsuperscript{18,19} This model describes the probability of AIH (Table 2).

**Table 2. International Diagnostic Criteria for the Diagnosis of AIH**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>+2</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Serum biochemistry</td>
<td></td>
</tr>
<tr>
<td>Ratio of elevation of serum alkaline phosphatase vs. aminotransferase</td>
<td></td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>−2</td>
</tr>
<tr>
<td>1.5–3</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>+2</td>
</tr>
<tr>
<td>Total serum globulin, γ-globulin, or IgG Times upper normal limit</td>
<td></td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>+3</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>+2</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>+1</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>0</td>
</tr>
<tr>
<td>Autoantibodies (titers by immunofluorescence on rodent tissues)</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>ANA, SMA, or LKM-1</td>
<td></td>
</tr>
<tr>
<td>&gt;1:80</td>
<td>+3</td>
</tr>
<tr>
<td>1:80</td>
<td>+2</td>
</tr>
<tr>
<td>1:40</td>
<td>+1</td>
</tr>
<tr>
<td>&lt;1:40</td>
<td>0</td>
</tr>
<tr>
<td>Antimitochondrial antibody</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>−4</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis viral markers</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>+3</td>
</tr>
<tr>
<td>Positive</td>
<td>−3</td>
</tr>
<tr>
<td>Other etiological factors</td>
<td></td>
</tr>
<tr>
<td>History of drug usage</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>−4</td>
</tr>
<tr>
<td>No</td>
<td>+1</td>
</tr>
<tr>
<td>Alcohol (average consumption)</td>
<td></td>
</tr>
<tr>
<td>&lt;25 g/day</td>
<td>+2</td>
</tr>
<tr>
<td>&gt;60 g/day</td>
<td>−2</td>
</tr>
<tr>
<td>Genetic factors: HLA DR3 or DR4</td>
<td></td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td></td>
</tr>
<tr>
<td>Response to therapy</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>+2</td>
</tr>
<tr>
<td>Relapse</td>
<td>+3</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
</tr>
<tr>
<td>Interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td>Predominant lymphoplasic infiltrate</td>
<td>+1</td>
</tr>
<tr>
<td>Rosetting of liver cells</td>
<td>+1</td>
</tr>
<tr>
<td>None of the above</td>
<td>−5</td>
</tr>
<tr>
<td>Biliary changes</td>
<td>−3</td>
</tr>
<tr>
<td>Other changes</td>
<td>−3</td>
</tr>
<tr>
<td>Seropositivity for other defined autoantibodies</td>
<td>+2</td>
</tr>
</tbody>
</table>

NOTE. Interpretation of aggregate scores: definite AIH, >15 before treatment and >17 after treatment; probable AIH, 10–15 before treatment and 12–17 after treatment. Data from Alvarez et al.\textsuperscript{19}
The validity of the score has been confirmed in 6 major studies evaluating a total of 983 patients. The overall sensitivity of the score to establish a diagnosis of definite or probable AIH was 89.8%, however, the specificity for discriminating AIH from overlapping syndromes such as with PBC and or with PSC was low. In a study applying the diagnostic criteria to patients with PSC, PBC, and autoimmune cholangitis (AMA-negative PBC), 37.1% were scored as probable AIH resulting in a specificity of only 60.8% for the exclusion of AIH in biliary disease. In the revised AIH score, patients with histologic and cholangiographic evidence of PBC or PSC should be viewed as variants of cholestatic diseases and not of AIH. Specifically, well-defined granulomas, typical bile duct pathology of PSC, and PBC and substantial marginal bile duct proliferation with cholangiolitis and copper accumulation exclude AIH. Cholangiography is recommended for all patients who score as definite or probable AIH but do not respond to standard steroid treatment.

### Histology

Although a disease-specific histologic feature does not characterize AIH, percutaneous liver biopsy should be performed when coagulation studies permit the procedure. Usually, histologic assessment shows periportal hepatitis with lymphocytic infiltrates, plasma cells, and piecemeal necroses. A lobular hepatitis can be present but is only indicative of AIH in the absence of copper deposits or biliary inflammation. Also, granulomas and iron deposits argue against AIH.

### Clinical Presentation of AIH

Based on limited epidemiologic data, the prevalence of AIH is estimated to range between 0.1 and 1.2 cases per 100,000 in Western Europe and North America among the white population but only 0.08–0.015 cases per 100,000 in Japan. In the North American and Western European white population, AIH accounts for about 20% of chronic hepatitis cases, and in Brazil only 5%–10% of patients with chronic hepatitis suffer from AIH. In about 25% of patients with AIH, an acute onset of AIH is observed, and rare cases of fulminant AIH have been reported. In most cases, however, the clinical presentation does not differ from that in other forms of chronic hepatitis and is characterized by fatigue, right upper quadrant pain, jaundice, and occasionally also by palmar erythema and spider nevi. In later stages, the consequences of portal hypertension dominate, including ascites, bleeding esophageal varices, and encephalopathy. A specific feature of AIH is the association of extrahepatic immune-mediated syndromes including autoimmune thyroiditis, rheumatoid arthritis, and diabetes mellitus (Table 3). Because many of the same extrahepatic manifestations are also present in chronic hepatitis C, hepatitis C virus (HCV) infection should be excluded.

### Natural History and Prognosis

The natural history and prognosis of AIH are largely defined by the inflammatory activity present at presentation and by the presence or development of cirrhosis. With a 5–10-fold elevation of aspartate aminotransferase and 2-fold γ-globulin elevation, mortality without treatment is 90% in 10 years. Of patients with periportal hepatitis, cirrhosis develops in 17% within 5 years, but cirrhosis develops in 82% when bridging necrosis or necrosis of multiple lobules is present. The presence of cirrhosis indicates a mortality of 58% in 5 years; however, the presence of cirrhosis at the beginning of treatment does not influence response or short-term outcome.

The course of AIH is also significantly influenced by the HLA antigen profile of the affected individual. The presence of HLA B8 is associated with severe inflammation at presentation and a higher likelihood of relapse after treatment. Individuals with HLA DR3 have a lower probability of reaching remission, have more frequent relapses, and require transplantation more often. The HLA DR4–positive subgroup is characterized by a higher age of onset and a more benign outcome.

Limiting confidence in assessments of the natural history of AIH, however, is the fact that frequently cited reports on the prognosis of AIH were written in the “pre hepatitis C era” based on data in a limited number of centers. These studies include placebo-controlled immunosuppressive treatment trials, the last of which was
published in 1980, at a time when only patients with severe chronic hepatitis were enrolled. Today, it is unethical to conduct placebo-controlled AIH trials, therefore, we may never accurately know the natural history of AIH diagnosed on the basis of contemporary internationally accepted diagnostic criteria that incorporate new autoantibody markers and sensitive diagnostic procedures for viral hepatitis.

**Autoantibodies in AIH**

The serologic hallmark of AIH are autoantibodies detected by serologic in vitro assays. For screening purposes, ANA, smooth muscle antibodies (SMA), LKM, and AMA continue to be determined by indirect immunofluorescence on rodent liver, stomach, and kidney tissue. When these autoantibodies are undetectable and the suspicion of AIH remains, autoantibodies against cytosolic antigens, in particular the SLA/liver-pancreas (LP) antigen, may be helpful. These SLA/LP autoantibodies are detected by radioimmunoassay and enzyme-linked immunosorbent assays (ELISAs) because they cannot be observed by immunofluorescence. In approximately 10% of patients with AIH, SLA autoantibodies are present as the only marker in the absence of the above-mentioned autoantibodies. For scientific purposes, autoantibody profiles have been used as a means of subclassification of AIH. According to this approach, AIH type 1 is characterized by the presence of ANA and/or anti-SMA directed predominantly against smooth muscle actin. AIH type 2 is characterized by anti–LKM-1 directed against cytochrome P450 (CYP) 2D6 and with lower frequency against uridine 5′-diphosphate glucuronosyltransferases. AIH type 3 is characterized by autoantibodies against SLA/LP, which have recently been identified as being directed against UGA-suppressor transfer RNA (tRNA)-associated protein and not against the previously suggested candidate autoantigens cytokeratins 8 and/or 18, or glutathione-S-transferases. Antibodies against LP and SLA autoantibodies seem to exhibit reactivity with the same UGA-suppressor tRNA-associated protein and not against the previously suggested candidate autoantigens cytokeratins 8 and/or 18, or glutathione-S-transferases. In addition, many cases of AIH display autoantibodies that show reactivity toward the asialoglycoprotein receptor and some reactivity with the liver cytosolic antigen 1 (LC-1), although these autoantibodies are not routinely determined. LC-1 autoantibodies are found in AIH type 2 and have been characterized as recognizing formiminotransferase cyclodeaminase (Table 4).

AIH type 1 (classical, lupoid AIH) represents the most common form of AIH, whereas AIH type 2 and 3 are rare entities. AIH type 2 displays a regionally variable prevalence with very low numbers in the United States.
but accounting for up to 20% of AIH cases in Western Europe. Clinically, the serologically defined AIH subtypes do not differ fundamentally. There is no good evidence that AIH type 1 and AIH type 3 are distinguishable on clinical grounds. However, the recognition of SLA/LP autoantibodies as markers of AIH in cases of ANA and LKM negativity, which is present in 10% of AIH cases, justifies recognition of this subset of patients and decreases the possibility of misdiagnosis. The differences between AIH type 1 and AIH type 2 are more apparent: In AIH type 2, patients are younger and more frequently display an acute onset of hepatitis with a more severe course and rapid progression than patients with AIH type 1 or 3. Although the IAHG strongly argues against a further subtyping of AIH, the distinction between type 1 and type 2 has already been widely adopted in clinical practice. Whether anti-SLA/LP antibodies characterize a special clinical subgroup will remain controversial until specific causative agents triggering AIH or subsets of the syndrome are identified.

ANA are directed against functional and structural components of the cell nucleus, against nuclear membranes, or DNA. The target antigens are heterogeneous and incompletely defined in AIH. For diagnostic purposes, the molecular characterization of target antigen specificity is not required. ANA are also detected in PBC, in which case they have been found to target gp 210, sp100, and nucleoprin p62. ANA are routinely determined by indirect immunofluorescence on cryostat sections of rat liver and on Hep.2 cell slides. Most commonly, a homogeneous or speckled immunofluorescence pattern is encountered. ANA have been found to react with centromeres, ribonucleoproteins, cyclin A, and many other antigens. They represent the most common autoantibody in AIH and occur in high titers usually exceeding 1:160. A subtyping of the various ANA specificities, which nowadays can be based on recombinant antigens, has no clinical significance. So far, neither liver-specific nuclear antigens nor liver disease-specific ANA have been identified.

Anti-SMA are directed against components of the cytoskeleton such as actin, troponin, and tropomyosin. They frequently occur in high titers in association with ANA. However, SMA autoantibodies also occur in advanced diseases of the liver of other causes, in infectious diseases, and rheumatic disorders. In these cases, titers are often lower than 1:80. SMA autoantibodies are also determined by indirect immunofluorescence on cryostat sections of rat stomach. SMA have been found to be generally associated with the HLA A1-B8-DR3 haplotype, and, possibly as a reflection of this HLA status, the affected patients are younger and have a poorer prognosis. Interestingly, the association of anti-actin-positive patients with HLA A1-B8-DR3 was stronger than the association of SMA-positive patients with this haplotype. Nonactin-positive patients with SMA showed a closer association with HLA DR4.

**LKM and Liver Microsomal Antibodies**

In 1973, Rizzetto discovered by indirect immunofluorescence autoantibodies reactive with the proximal renal tubule and the hepatocellular cytoplasm. These autoantibodies termed LKM-1 are regarded as markers of a second form of AIH. Between 1988 and 1991, the 50-kilodalton antigen of LKM-1 autoantibodies was identified as cytochrome P450 2D6 (CYP2D6). LKM-1 autoantibodies recognize a major linear epitope between amino acids 263 and 270 of the CYP2D6 protein. These autoantibodies inhibit CYP2D6 activity in vitro and are capable of activating liver infiltrating T lymphocytes. This observation suggests a combined humoral and cellular immune mechanism leading to the development of LKM autoantibodies. In addition to linear epitopes, LKM-1 autoantibodies have also been shown to recognize conformation-dependent epitopes. However, the recognition of epitopes located between amino acids 257–269 seems to be a specific autoimmune reaction associated with AIH and discriminates between LKM-1 autoantibodies associated with AIH and those associated with chronic HCV infection. CYP2D6 has been found to be expressed on the hepatocellular surface, and its expression seems to be regulated by cytokines.

Antibodies against microsomal proteins form a heterogeneous group spanning several immune-mediated diseases including AIH, drug-induced hepatitis, autoimmune polyglandular syndrome type 1 (APS-1), and chronic hepatitis C (HCV) and D (HDV). Antimicrosomal autoantibodies against CYP1A2 and CYP2A6 are found in patients with the autoimmune polyglandular syndrome type 1 (APS-1) with hepatic involvement. Anti-CYP2A6 autoantibodies also occur in HCV infection. Liver microsomal autoantibodies, which are characterized by an immunofluorescence pattern selectively staining the hepatocellular but not renal cytoplasm, have been found to be directed against CYP1A2, CYP2A6, and CYP2C9 and are induced in ticrynafen-associated hepatitis. A second type of LKM autoantibodies, LKM-2, is directed against CYP2C9 and are induced in ticrynafen-associated hepatitis. A third group of LKM autoantibodies, LKM-3, was identified in 6%–10% of patients with chronic HDV...
infection by Crivelli 1983. These autoantibodies are directed against family 1 uridine 5’-diphosphate glucuronosyltransferases (UGT1A), which are also a superfamily of drug metabolizing proteins located in the endoplasmic reticulum. LKM-3 autoantibodies have been identified in HDV infection but also in AIH type 2 patients. They can also occur in LKM-1-negative and ANA-negative AIH.

In addition, LKM-positive sera display reactivity with a number of currently undefined antigens with molecular weights of 35, 57, 59, and 70 kilodaltons. These autoantibodies are predominantly found in AIH, HCV infection, and halothane hepatitis.

LKM autoantibodies are visualized by indirect immunofluorescence on rodent cryostat sections. Subclassification is achieved by ELISA and Western blot, preferably with recombinant antigens.

Antibodies against SLA/LP were detected in a patient with ANA-negative AIH and are directed against UGA-suppressor tRNA-associated protein. The exact function of this protein and its role in autoimmunity are unclear. In earlier reports, reactivity with cytokeratins 8 and 18 as well as with glutathione-S-transferase were detected, which was not confirmed in later studies. SLA autoantibodies are highly specific for AIH. Recent studies have also shown that SLA autoantibodies are reactive with the same antigen as the independently described liver-pancreas autoantibodies (anti-LP). This has led to the designation of SLA/LP autoantibodies that are detected by ELISA (Table 5). In about 75% of cases, SLA/LP autoantibodies occur simultaneously with other autoantibodies such as SMA and are more rarely with AMA. In ANA-positive patients, SLA autoantibodies appear in 11% of cases. SLA/LP autoantibodies are detected by ELISA (Table 4).

**Other Autoantibodies in AIH**

The asialoglycoprotein receptor is a liver-specific glycoprotein located in the cell membrane. Autoimmunity targeting this antigen is observed in 88% of all patients with AIH; however, anti-asialoglycoprotein receptor antibodies are also found in chronic hepatitis B and C, alcoholic liver disease, and PBC. The levels of anti-asialoglycoprotein receptor antibodies fluctuate according to inflammatory activity of the disease and can be viewed as an additional marker to monitor therapeutic efficacy. Anti-asialoglycoprotein receptor seems to be a general marker of liver autoimmunity. They are not routinely used for diagnostic purposes.

Anti–cytosol autoantibodies type 1 (anti–LC-1) antibodies are viewed as a second marker of AIH type 2, in which they have been detected in up to 50% of LKM-positive sera. Other data indicate their occurrence in combination with ANA and SMA autoantibodies and in chronic hepatitis C. Contrary to LKM autoantibodies, LC-1 autoantibodies seem to correlate with disease activity. The molecular antigen target has been identified to be formiminotransferase cyclodeaminase, but the clinical significance has not yet been completely defined.

Antineutrophil cytoplasmic autoantibodies (ANCA) are detected in 65%–96% of sera from patients with AIH type 1. Immunofluorescence distinguished 2 major ANCA patterns: cANCA with a diffuse cytoplasmic staining of neutrophils and pANCA, which exhibit a rim-like staining of the perinuclear cytoplasm. Among the major autoantigen targets with diagnostic clinical relevance are myeloperoxidase (pANCA), which are detected in 60%–80% of patients with microscopic polyangiitis, and proteinase 3 (classical cANCA), which is closely associated with Wegener’s granulomatosis. In AIH, atypical pANCA (also termed xANCA) are usually detected that display a pANCA immunofluorescence pattern but do not show reactivity with myeloperoxidase. ANCA are rarely detected in AIH type 2. The discrimination of ANCA and ANA is difficult because ANA frequently also stain ethanol-fixed neutrophils. Most likely the presence of ANCA is only accurate if the ANCA titer exceeds that of ANA by 2-fold. The role of ANCA in AIH is not clear and their routine determination is not recommended.
Classification and Subclassification of AIH as a Clinical Challenge

For years, the existence of AIH as a separate hepatic disease was a matter of intense debate. Currently, however, controversy surrounds the question of whether AIH is heterogeneous in nature, as discussed above. There are 2 ways to define heterogeneity in AIH: for many years, autoantibodies have been used to distinguish subtypes of AIH; however, the IAHG regards such distinctions to be too premature for routine use in everyday practice. The other way to classify the heterogeneity of AIH is based on immunogenetics.

The Challenge of Genetic Heterogeneity

Not only the prevalence of but also the immunogenetic associations with AIH vary regionally. AIH in whites has an association with HLA DRB1*0301. In Japan, the A1-B8-DR3 haplotype is almost absent, and a typical association with HLA DRB1*0405 has been found. Argentinean adults with AIH have an increased frequency of HLA DRB1*0405 and Mexicans of HLA DRB1*0404. In children from Argentina and Brazil, a strong association with HLA DRB1*1301 and a weaker association with DRB1*0301 have been demonstrated. These data suggest evolutionary differences in the prevalence of and susceptibility to AIH. From these findings, it can be expected that a number of genetic associations are responsible for AIH. However, the genetic data presently available argue strongly for a genetic predisposition for disease progression rather than disease susceptibility. AIH is a polygenetic disease. Many genetic markers are being identified, each of which contributes a small piece of the puzzle.

The Challenge of Immunoserological Heterogeneity

AIH Type 1

Representing 80% of the cases of AIH, this form is the most prevalent subclass. Seventy percent of patients are female with a peak incidence between ages 16 and 30 years. However, 50% are older than 30 years. An association with other immune syndromes is observed in 48%, including autoimmune thyroid disease, synovitis, and ulcerative colitis. The clinical course is often unremarkable, and acute onset is very rare. About 25% have cirrhosis at the time of diagnosis.

AIH Type 2

Serum immunoglobulin levels are moderately elevated with a reduction of immunoglobulin A. AIH type 2 is a rare disorder that affects 20% of AIH patients in Europe but only 4% in the United States. There is a female predominance. The number of extrahepatic immune syndromes such as diabetes, vitiligo, and autoimmune thyroid disease is more prevalent than in AIH type 1. The average age at the time of diagnosis is around 10 years, but AIH type 2 is also observed in adults, especially in Europe. AIH type 2 carries a higher risk of progression to cirrhosis and of a fulminant course at onset.

AIH Type 3

AIH type 3 is the most controversial of all serologic subgroups. AIH type 3 has a lower prevalence than AIH type 2, 90% of cases are females, and the age maximum is between 20 and 40 years. This subclass of AIH resembles AIH type 1 with respect to clinical characteristics, immunogenetic markers, and treatment response. The detection of autoantibodies against UGA-suppressor tRNA-associated protein, which is very specific for AIH, makes this defined entity an attractive model to study the molecular origin of AIH.

Differential Diagnosis

Cryptogenic hepatitis is an etiologically undefined chronic hepatitis. Patients with cryptogenic hepatitis are negative for viral as well as autoantibody markers. It is not established how many of these patients suffer from AIH without detectable autoantibodies. In about 13% of patients, initially seronegative when tested by indirect immunofluorescence for ANA, SMA, and LKM, detection of SLA autoantibodies contributed to their diagnostic clarification. Clinically this group of patients with cryptogenic hepatitis resembles AIH type 1 with respect to age and sex distribution, HLA antigen types, inflammatory activity, and response to therapy. Overlap syndromes are conditions in which there are leading symptoms of AIH, but additional markers and symptoms point to other liver diseases. The “overlap syndrome” is a descriptively vague designation of syndromes in which patients present with clinical, histologic, and immunoserological signs of AIH and one of the cholestatic autoimmune liver diseases, either PBC or PSC. The following terms have been used: immune cholangitis, PBC/CAH overlap syndrome, or AIH/PSC overlap syndrome.
In one of the series reported, patients had serologic markers of PBC in 8% with serum AMA and histologic signs of nonsuppurative cholangitis, PSC in 6% with typical changes of the biliary tree by cholangiography, and autoimmune cholangitis in 10% with ANA, SMA, and histologic inflammation of the biliary system.20

Virus-Associated Autoimmunity

Another clinically relevant overlap situation is virus-associated autoimmunity, characterized by the occurrence of significant titers of autoantibodies in viral hepatitis.4,13 Autoantibodies are found in all types of viral hepatitis, and the prevalence varies geographically. Autoantibodies, including antithyroid antibodies, may occur at significant titers spontaneously or during interferon treatment.113 The coexistence of AIH and viral hepatitis is a rare event although documented in the literature. Also, subclinical autoimmune liver disease may become manifest very rarely when patients with viral hepatitis, in particular those with hepatitis C, are treated with cytokines.89 On the other hand, it has been well documented that several patients with chronic hepatitis C and significant titers of autoantibodies, in particular those from France, Spain, Italy, Japan, Germany, and other countries, may experience an increase of aminotransferase levels, and some of these patients may require immunosuppression. Autoimmune mechanisms are being considered as an explanation for these rare exacerbations. In general, patients with replicating chronic viral hepatitis should be treated initially with antivirals, but should be monitored more carefully than those without significant autoantibody titers detectable in serum.

The best-studied associations at a molecular level are HCV and HDV infections in which LKM autoantibodies can be detected in 2%–5% and 6%–12% of cases, respectively. AIH type 2 and HCV infection with LKM autoantibodies are clinically distinct entities.114,115 LKM autoantibodies in virus infection are present at lower titers and recognize more conformational and diverse epitopes than those in genuine AIH. This distinction is relevant because it forms the basis for mutually exclusive therapeutic strategies, immunosuppression in AIH, and interferon in chronic virus hepatitis.77

APS-1

Hepatitis has also been described in 10%–15% of patients with APS-1.116,117 This syndrome is characterized by mucocutaneous candidiasis, hypothyroidism, Addison’s disease, and other endocrinopathies.118,119 In patients with APS-1, autoantibodies to CYP1A2 and CYP2A6 have been described as markers of an autoimmune liver disease.86,87 Anti-CYP1A2 antibodies are associated with the occurrence of hepatitis, whereas anti CYP2A6, a cytochrome that is not exclusively expressed in liver, also occurs in patients with APS-1 that do not suffer from liver disease.

Indications for Therapy: The Challenge of Whom to Treat

An absolute indication for treatment is present in acute-onset or fulminant AIH, when aminotransferase levels exceed 5–10 times the upper normal value, upon histologic evidence of bridging or multilobular necrosis, as well as when severe hepatic and extrahepatic symptoms (fatigue, upper right quadrant pain, associated immune-mediated symptoms) are present.31 In the presence of mild disease activity such as aminotransferase levels below 5–10-fold elevation, hepatitis lacking fibrosis, and mild symptoms of hepatitis, the indications for treatment must be weighed individually against the risks associated with therapy. Analyses have shown that hepatitis in the absence of fibrosis is associated with only a low risk of developing cirrhosis and therefore may result in unaltered life expectancies even if left untreated. When aminotransferase levels are only mildly elevated, histology shows inactive cirrhotic changes, but when active inflammation is absent, an indication for immunosuppressive therapy is not present. Liver failure inevitably leads to consideration for liver transplantation as the definitive therapeutic measure.31

Treatment of AIH

AIH was the first chronic liver disease in which medical treatment was shown to prolong survival. Two fundamental goals are distinguished: induction of remission and maintenance of remission.

Induction of Remission: Standard Immunosuppressive Treatment

The standard initial treatment of AIH is prednisone monotherapy or combination therapy with prednisone and azathioprine.120 Both are equally effective.41,121 Prednisolone or prednisone can both be used and are equally effective. Decrease of liver function in cirrhosis does not affect the metabolism from prednisone to prednisolone. Combination therapy is generally preferred because of the marked reduction in unwanted side effects in this group. The decision for either strategy involves the consideration of patient profiles (Table 5): combination therapy is best suited for elderly, osteoporotic patients, patients with a metabolic syndrome (diabetes, hypertension, obesity), and with psychiatric labil-
Conversely, monotherapy with steroids would be preferred in patients with hematologic abnormalities (cytopenia), for short treatment trials when response to immunosuppressive treatment is used as a diagnostic procedure and in young patients when fertility becomes an issue. While corticosteroids are as effective as combination treatment to induce remission, azathioprine monotherapy is ineffective for inducing remission. The issue of azathioprine teratogenicity and oncogenicity requires discussion with young patients. Although in animal models teratogenicity and oncogenicity have been observed, this has not been conclusively shown in humans. Nevertheless, teratogenicity and oncogenicity cannot be ruled out and therefore azathioprine therapy during pregnancy cannot be recommended.

Treatment should generally follow defined therapeutic schedules (Table 6). However, in individual patients therapy is best tailored to the patient's presentation. This is particularly true in elderly patients with low inflammatory activity who may best remain untreated. The table reflects the Mayo approach. In our experience, monotherapy with prednisone beginning with 50 mg and tapered by 10 mg every 10 days to a maintenance dose of 15–20 mg, and alternatively combination therapy with 1 mg/kg body wt of azathioprine for 3 weeks and tapering to 50 mg daily combined with prednisone therapy tapered to 10 mg daily, are equally effective. There is no published evidence of an advantage of an individual tapering regimen, and different tapering and dosing regimens are used by different centers. In the individual young patient without severe symptoms and with low inflammatory activity (biopsy, ALT < 5× upper limit of normal), treatment can be initiated with maintenance doses.

Table 6. Treatment Regimen and Follow-Up Examinations of AIH Regardless of Autoantibody Type

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>60 mg reduction within 4 weeks to maintenance dose 20 mg or lower</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>(maintenance with azathioprine: monotherapy: 2 mg/kg body wt)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Reduction of daily dose by 2.5 mg per week</td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examination</th>
<th>Before therapy</th>
<th>During therapy before remission</th>
<th>Remission under therapy q 3–6 months</th>
<th>Cessation of therapy Remission post therapy q 3–6 months</th>
<th>Evaluation of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>+</td>
<td>(+/-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blood count</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>γ-Glutamyltransferase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>γ-Globulin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coagulation studies</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NOTE. In the elderly patient with low inflammatory activity, the indication to treat must be weighed against side effects and many of these patients may best remain untreated. The table reflects the Mayo approach. In our experience, monotherapy with prednisone beginning with 50 mg and tapered by 10 mg every 10 days to a maintenance dose of 15–20 mg, and alternatively combination therapy with 1 mg/kg body wt of azathioprine for 3 weeks and tapering to 50 mg daily combined with prednisone therapy tapered to 10 mg daily, are equally effective. There is no published evidence of an advantage of an individual tapering regimen, and different tapering and dosing regimens are used by different centers. In the individual young patient without severe symptoms and with low inflammatory activity (biopsy, ALT < 5× upper limit of normal), treatment can be initiated with maintenance doses.

NA, not applicable.
pressive therapy is documented, the risk of relapse is only 20%. In biopsy specimens showing portal hepatitis, relapse occurs in 50% within 6 months after end of treatment. However, if treated patients progress to cirrhosis or show signs of interface hepatitis, relapse is invariably observed after the end of treatment. Overall, the frequency of relapse is 50% in 6 months and 70% in 3 years after withdrawal of immunosuppressive therapy. A sustained response is achieved in only 17% of patients. Azathioprine maintenance after prednisone withdrawal reduces the likelihood of relapse.

No or Incomplete Remission With Standard Immunosuppression: The Difficult-to-Treat Patient as a Particular Challenge (Role of Maintenance Therapy)

Other typical treatment end points in AIH are an incomplete response in which no remission is reached within 2 years of treatment, treatment failure in which biochemical and clinical signs of AIH deteriorate during therapy, and intolerance of the administered drugs. The standard treatment schedules have to be altered in these situations. When incomplete responses are present, immunosuppression is usually required indefinitely at the lowest possible dose to maintain aminotransferase levels below 5 times the upper limit of normal or to reach histologic remission. This can be achieved by combination therapy with prednisone and azathioprine, or by indefinite therapy with azathioprine alone (2 mg · kg\(^{-1}\) · day\(^{-1}\)). Treatment failure usually requires a trial with high-dose corticosteroids (60 mg/day) or combination therapy (30 mg prednisolone and 150 mg azathioprine per day) for 4–6 weeks. In 20% of patients, liver failure is a risk that leads to consideration of liver transplantation. Drug intolerance calls for an immediate reduction of the implicated drug and the determination of the single tolerated drug capable of controlling the disease. Usually, vertebral compression, psychosis, diabetic decompensation, or severe weight gain are complications of steroid therapy, which can be overcome by increasing the azathioprine dose or by azathioprine maintenance therapy. Severe cytopenia, arthralgia, and myalgia may be complications of azathioprine (Table 5).

If treatment results are unsatisfactory, alternative drugs such as cyclosporin A, tacrolimus, cyclophosphamide, mercaptopurine, mycophenolate mofetil, or the addition of ursodeoxycholic acid can be considered; however, efficacy in clinical trials has not been shown (see below).

Treatment Options in Difficult-to-Treat Patients

The therapy of AIH with prednis(ol)one and azathioprine is not ideal, and the search for drugs with a favorable risk-benefit ratio is ongoing. For most of the alternative approaches, the results have been disappointing and the adverse effects severe. Therapeutic goals include the prevention of treatment failure, the achievement of long-term remission with the prevention of corticosteroid side effects, and the treatment of overlap disorders.

The Challenge of Preventing Treatment Failures

Tacrolimus

FK506 is a potent macrolide lactone compound with immunosuppressive capabilities exceeding those of cyclosporin A. The application of 3 mg twice a day in 21 patients treated for 1 year led to an improvement of aminotransferase and bilirubin levels. Although FK506 represents a promising immunosuppressive candidate drug, larger randomized trials are required to assess its role in the therapy of AIH.

Cyclosporin A

Cyclosporin A is a lipophylic cyclic peptide of 11 residues produced by Tolypocladium inflatum that acts on calcium-dependent signaling and inhibits T-cell function via the interleukin 2 gene. In a recent study, treatment of 32 children with AIH type 1 and 4 children with AIH type 2 resulted in histologic improvement at doses of 2–3 mg · kg\(^{-1}\) · day\(^{-1}\). There was no difference in response between AIH type 1 and AIH type 2. Although relapses did not occur in a separate study of 15 patients with AIH type 2, this was not observed in an earlier trial. Cyclosporin A seems to be well tolerated in AIH.

Cyclophosphamide

The induction of remission with 1–1.5 mg · kg\(^{-1}\) · day\(^{-1}\) in combination with steroids has been reported. However, the dependency of continued application of cyclophosphamide with its potentially severe hematologic side effects renders it a highly experimental treatment option.

Mycophenolate

Mycophenolate-mofetil has received attention as a transplant immunosuppressant with an important role in the steroid-free immunosuppressive therapy of patients
transplanted with chronic hepatitis C infection. In a recent pilot study, 7 patients with AIH type 1 who either did not tolerate azathioprine or did not respond to standard therapy with a complete normalization of aminotransferase levels were treated with 1 g of mycophenolate-mofetil twice a day in addition to steroids, and followed for a median of 46 months. In 5 of 7 patients, normalization of aminotransferase levels was achieved within 3 months. One patient developed leukopenia. These preliminary data suggest that mycophenolate-mofetil may represent another alternative strategy of preventing treatment failure. Larger studies are required to provide more evidence for a beneficial effect.

The Challenge of Achieving Long-term Remission Without Corticosteroid Side Effects

Budesonide

Budesonide is a synthetic steroid with high first-pass metabolism in the liver, which should limit systemic side effects compared with conventional steroids. It is a common drug for allergic pulmonary disease. In a study treating 13 AIH patients with 6–8 mg of budesonide per day over a period of 9 months, the drug was well tolerated and aminotransferase levels were normalized. Our own experiences have confirmed that budesonide is effective but does not offer an advantage over conventional steroids when cirrhosis and portosystemic shunts are present. Remission can be achieved when budesonide is used instead of prednisolone. However, the main advantage of budesonide for the future treatment of AIH is to replace prednisolone in long-term maintenance therapy to reduce steroid side effects. This potential benefit has not been realized in clinical trials.

Azathioprine

Azathioprine is effective in maintaining remission after remission has been achieved by combination or corticosteroid monotherapy and represents a corticosteroid-free alternative as discussed above. Induction of remission with azathioprine monotherapy is not effective, as discussed above.

The Challenge of Cholestatic Disease and AIH

Ursodeoxycholic Acid

Ursodeoxycholic acid is a hydrophilic bile acid with putative immunomodulatory capabilities. It is presumed to alter HLA class I antigen expression on cellular surfaces and to suppress immunoglobulin production. Uncontrolled trials have shown a reduction in histologic abnormalities and clinical and biochemical improvement but not a reduction of fibrosis in 4 patients with AIH type 1 given 600 mg/day over 2 years. In contrast, no benefit was reported when 13–15 mg · kg⁻¹ · day⁻¹ was given. Ursodeoxycholic acid is a well-tolerated drug; however, its role in AIH therapy or in combination with immunosuppressive therapy is still unclear.

Non-Liver Disease–Specific Therapy, Therapy of Complications

Demineralization

Steroid treatment has a negative impact on bone mineralization. Supplementation with vitamin D, calcium, and regular physical activity should accompany therapy routinely. In postmenopausal women, hormone replacement therapy is indicated. Whether bisphosphonate therapy of symptomatic osteoporosis is beneficial in chronic liver disease of noncholestatic cause is presently unclear.

Vitamin Replacement

Vitamin K (if indicated by coagulation studies) and multivitamin supplements should be administered.

Liver Transplantation

Transplantation is the treatment option of choice in end stage AIH. There is no single indicator that predicts that liver transplantation will be required in patients with AIH. Candidates for liver transplantation are usually among the treatment failure group in whom cirrhosis progresses despite immunosuppressive therapy. Patients who do not reach remission within 4 years of continuous therapy are at elevated risk for liver failure and should therefore be evaluated for liver transplantation. Indicators of a high mortality associated with liver failure are histologic evidence of multilobular necrosis and progressive hyperbilirubinemia.

In Europe, 4% of liver transplants are for AIH. The 5-year survival is 92%, and the recurrence of AIH is estimated to range between 11% and 35%. The persistence of autoantibodies does not indicate or predict recurrence of AIH. Individual adjustment of immunosuppressive therapy after transplantation in patients with AIH is necessary to prevent or control recurrence of AIH. De novo development of AIH after retransplantation has been reported.

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