Autoimmune Liver Disease

Heiner Wedemeyer, MD and Michael P. Manns, MD

Hannover Medical School
Hannover, Germany

Key Concepts

- The diagnosis of autoimmune hepatitis is based on specific immunological, histological and biochemical characteristics after exclusion of other causes of liver disease including viral hepatitis.
- Hepatitis E virus infection should be considered in the differential diagnosis of autoimmune hepatitis.
- Prednisone, prednisolone, or budesonide are first line treatment options for autoimmune hepatitis with or without addition of azathioprine. Treatment is indefinite in the majority of patients.
- Detection of antimitochondrial antibodies is a hallmark of for the diagnosis of primary biliary cirrhosis.
- Ursodeoxycholic acid is indicated for the treatment of primary biliary cirrhosis leading to improved clinical long-term outcome.
- Overlap syndromes can occur between the different cholestatic liver diseases and AIH and may show dynamic patterns over time with changes in the dominant disease. Individualized treatment approaches are required.

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is an inflammatory chronic liver disease which is caused by a loss of tolerance against hepatic tissue. The tight balance between tolerance and auto-aggression can be modulated and disturbed by various internal factors. It is therefore in general not possible to determine the specific cause for clinical manifestation of AIH in individual patients. Females are more likely to develop AIH and all ethnic groups can be affected. The genetic background of AIH is rather polygenic. Human leukocyte antigens (HLA) DRB1*0301 and DRB*0401 seem to confer susceptibility to AIH in Caucasian patients (4). Other HLA types are associated with severity of liver disease or response to therapy. Additional single nucleotide polymorphisms have been linked to AIH (12) including vitamin D receptor polymorphisms (17). AIH can be part of a genetic disorder called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) which is caused by specific mutations in the AIRE gene. This represents the only condition where counselling of family members is warranted as it is otherwise unlikely that a significant risk for AIH is transmitted to subsequent generations.

Already 20 years ago it was postulated that viral infections may trigger clinical onset of autoimmune hepatitis, e.g., an association has been described between herpes simplex virus 1 infection and autoimmune hepatitis. Other infectious agents including hepatitis C virus (HCV), cytomegalovirus, human T lymphotropic viruses 1 and 2 or salmonella typhimurium have been suggested to induce autoimmune liver disease. Recently, we reported higher anti-hepatitis E virus (HEV) prevalence rates in patients...
with AIH but not in individuals with another autoimmune disease. (Pischke et al., EASL 2013; data will be presented). Higher anti-HEV frequencies maybe suggest that HEV infection could initiate onset of AIH but also be the consequence of AIH misdiagnosis if acute hepatitis E has not been ruled out. Histological features of AIH may show similar characteristics to HEV infection (18;19).

**Diagnosis of AIH**

The diagnosis of AIH is based on criteria developed by an International Expert panel first published in 1993 and revised in 1999 (16). These criteria include gender, serum biochemistry (ratio between serum alkaline phosphatase and alanine aminotransferase), serum immunoglobulin levels, liver histology, presence of absence of specific autoantibodies, absence of hepatitis virus markers and other causes of liver disease alcohol consumption, and response to immunosuppressive treatment. The histological hallmark of AIH is an interface hepatitis with plasma cell infiltration. However and importantly, there is not a specific histological finding in AIH and even the absence of plasma cells does not preclude the diagnosis of AIH. Typical autoantibodies in AIH are ANA, SMA, anti-LKM1 (specifically antibodies against cytochrome P4502D6) and anti-LC1 (targeting formiminotransferase cyclo deaminase (FTCD)). Autoantibodies are not specific to AIH. While ANA and SMA lead to the diagnosis of AIH-type 1, LKM1 and LC1 antibodies are found in AIH-type 2. Presence of some autoantibodies such as LC1 or SLA may have prognostic implications (21).

A more simple score based on autoantibodies, IgG concentrations, histology and absence of viral hepatitis proved high sensitivity and specificity in independent cohorts and should therefore be validated prospectively (8;23).

**Natural History of AIH**

Severe acute onset of AIH with liver enzymes elevated at least 10-fold upper the limit of normal is associated with a high mortality of up to 60% after 6 months of follow-up if untreated (12). Thus, there is an absolute indication to initiate immunosuppressive therapy in these patients. About 20% of patients severe acute AIH may fail to respond to corticosteroid therapy and transplantation may be the only remaining treatment option (24). Presence of bridging necrosis is also associated with a significant risk for disease progression and mortality and should therefore also be treated early. In contrast, there is limited data on the natural history in asymptomatic patients with mild liver disease and is difficult to identify patients with a benign course. “Spontaneous resolution” of AIH is also possible. There is some evidence that the long-term survival may be lower in untreated asymptomatic patients than in treated individuals but the risk for potential treatment-associated side-effects must be taken into account before immunosuppressive therapy is initiated. Most guidelines recommend to consider treatment in adult patients without symptoms and mild biochemical and histology disease activity.

Hepatocellular carcinoma develops at lower frequencies in patients with AIH as compared to patients with viral hepatitis or NASH. However, cases have been described and the 10-year probability for HCC is around 3% in AIH (22). Thus, regular HCC screening is recommended for patients with liver cirrhosis.

**Treatment of AIH**

Corticosteroids are effective in most patients with AIH to induce remission (12). Both prednisone and prednisolone can be used as first line treatment either alone or in combination with azathioprine. Different dosing regimens have been used in the United States and Europe which will be presented in detail during the presentation. Tapering of the steroid dose should be performed every 1-2 weeks down to an individual level able to maintain remission. The advantage of adding azathioprine can be to reduce occurrence of corticosteroid-related side effects and can be used at a fixed dose of 50mg (preferred in the United Stated) or 1-2mg/kg body weight (widely used in Europe).

Budesonide (6-9 mg per day) has been shown to induce remission in non-cirrhotic patients with autoimmune hepatitis in combination with azathioprine in a large international randomized trial (13). 60% of patients showed a complete biochemical remission after 6 months which

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>+2</td>
<td>HLA DR 3 or DR4</td>
<td>+1</td>
</tr>
<tr>
<td>AP:AST ratio &gt;3/ &lt; 1.5</td>
<td>-2/+2</td>
<td>Viral Markers pos / neg</td>
<td>-3/+3</td>
</tr>
<tr>
<td>IgG levels</td>
<td>+3/+2/+1</td>
<td>Alcohol</td>
<td>+2/-2</td>
</tr>
<tr>
<td>&gt;2/1.5-2.0/1.0-1.5 x ULN</td>
<td>&lt;25/ &gt;60 g/day</td>
<td>Drugs yes / no</td>
<td>-4/+1</td>
</tr>
<tr>
<td>AMA positivity</td>
<td>-4</td>
<td>Other antibodies</td>
<td>+2</td>
</tr>
<tr>
<td>&gt;1:80/1:80/1:40</td>
<td>+3/+2/+1</td>
<td>(SLA, anti LC1, etc.)</td>
<td>+2</td>
</tr>
<tr>
<td>Histology: Interface hepatitis</td>
<td>+3</td>
<td>Histology: plasmocytic</td>
<td>+1</td>
</tr>
<tr>
<td>Histology: rosettes</td>
<td>+</td>
<td>Histology: biliary features</td>
<td>-3</td>
</tr>
<tr>
<td>Histology: absence of interface/rosettes/plasmocytic</td>
<td>-5</td>
<td>Treatment response: complete / relapse</td>
<td>+2/+3</td>
</tr>
</tbody>
</table>

Definite Diagnosis: >15 points (17 after treatment); Probable 10-15 (12-17 after treatment)
was more common than in the control group receiving prednisone (39%). Moreover, steroid-specific side-effects were less frequent in patients receiving budesonide. Budesonide may also be considered for maintenance therapy after initial remission has been achieved with prednisone. However, budesonide should not be given to patients with liver cirrhosis as thrombotic events may be more associated with therapy (14).

Treatment response is defined by normalisation of AST, bilirubin and gamma-globulin levels. Biochemical endpoints with values <2x upper the limit of normal should not be accepted (12). Importantly, histological improvement is much slower as compared to biochemical improvement and treatment should therefore be stopped only after more than 2-3 years with normal biochemical values. The majority of patients will develop a relapse and long-term maintenance therapy is usually required in these cases.

Alternative immunosuppressive drugs have been used for patients not-responding to standard immunosuppression or experiencing relapses. Cyclosporine, tacrolimus, 6-mercaptopturine, methotrexate, cyclophosphamide, mycophenolate mofetil and ursodeoxycholic acid have been explored mostly in uncontrolled and small case series (12). Currently, mycophenolate is the most promising agent with the most robust data available but side effects and intolerance to the drug need to be considered (25). Very recently, infliximab has been used successfully used as a rescue therapy in a series of 11 difficult-to-treat AIH patients (20) which certainly needs to be confirmed in larger trials.

**Table 2:** Treatment options for autoimmune hepatitis

<table>
<thead>
<tr>
<th>First line treatment</th>
<th>Dose / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone or prednisolone monotherapy</td>
<td>Start: 60mg/day; 2nd week 40mg/day</td>
</tr>
<tr>
<td>Prednisone/azathioprine combination</td>
<td>Start: 30mg PRED / 50mg (1-2mg/kg/d) AZA</td>
</tr>
<tr>
<td>Budesonide/azathioprine combination (non-cirrhotics only)</td>
<td>Budesonide: 6-9mg/day + AZA 1-2 mg/kg/d</td>
</tr>
</tbody>
</table>

but the outcome of pregnancy is still better than in many other chronic diseases including diabetes (7;12).

Patients with chronic hepatitis C may also develop features of AIH. Antiviral therapy with interferon alpha may lead to exacerbation of AIH (5) but the risk is very low. Future interferon-free therapies of hepatitis C should therefore be preferred in individuals with AIH.

**Primary Biliary Cirrhosis**

Primary biliary cirrhosis is an autoimmune liver disease with inflammation of small bile ducts caused by humoral and cellular immune responses targeting mitochondrial autoantigens, specifically PDC-E2 (9). Genome-wide association studies as well as mouse models of PBC revealed an important role of the IL-12 pathway in the pathogenesis of PBC (11).

The diagnosis of primary biliary cirrhosis (PBC) is based on the presence of antimitochondrial antibodies (AMA) and elevation of serum alkaline phosphatase (AP) levels for more than 6 months (1;10). Improved sensitivity and specificity of autoantibody testing has been achieved by the development of tests against the mitochondrial target auf AMA (PDC-E2, or anti-AMA-M2). ANA can be detected in 30% of PBC patients. Specific immunofluorescence patterns ANA (nuclear dots and perinuclear rims) show a high specificity for PBC. Liver histology is not required to establish the diagnosis PBC but can be useful for grading and staging of liver disease. Granuloma formation and focal duct obliteration are histological hallmarks of PBC. Abdominal ultrasound is mandatory to exclude bile duct dilatation or focal liver lesions as a cause of elevated cholestatic enzymes.

**Natural History of PBC**

The natural history of PBC has been studied in different cohorts recruited in North America and Europe. Between 40% and 90% of asymptomatic PBV patients eventually became symptomatic after 5-19 years of follow-up. In the absence of ursodeoxycholic acid therapies, survival of patients with PBC was reduced compared to healthy populations with 10 year survivals between 50% and 70% (15).

Pruritus is one of leading symptoms in PBC which is often difficult to treat. Ursodeoxycholic acid does not improve pruritus but, paradoxically, may even worsen symptoms. The stepwise approach to treat pruritus in PBC should therefore include reducing UDCA. Guidelines usually recommend cholestyramine as a first line treatment of pruritus, followed by the PXR agonist rifampicin, oral.
opiate antagonists or sertaline as third line therapy and experimental treatments including artificial liver support systems as last options (1).

Women are more likely to suffer from fatigue which is independent from biochemical activity of PBC (3). There are no specific treatments available for fatigue in PBC and symptoms may even persist after liver transplantation.

Treatment of PBC

Patients with PBC should receive therapy with ursodeoxycholic acid (UDCA), usually at a dose of 13-15 mg/kg/day (1;10). Biochemical response defined by normalisation or improvements of bilirubin, AP and AST levels are associated with a favourable long-term outcome. Age is associated with response to UDCA therapy while male sex is an independent predictor of nonresponse (3). Treatment options for patients not-responding to UDCA therapy are limited. Combination of UDCA with budesonide has been suggested for non-cirrhotic patients but there is no consensus or general recommendation. Liver transplantation remains the only treatment for patients with advanced disease. Long-term outcome after liver transplantation for PBC is very good. Recurrence of PBC has been described in up to one-fifths of patients but the course is usually benign (6).

Overlap Syndromes

Some patients may present with symptoms of both autoimmune hepatitis and cholestatic disorders including PBC or PSC (2). “Overlap syndromes” may also develop over time and few patients with AIH develop overlap features after decades. The frequency of overlap syndromes are may range between 0% and 20% depending on the scoring system applied. Diagnosis of AIH-PBC overlap requires presence of at least 2 of 3 key criteria for both PBC (AP >2xULN; AMA >1:40; bile duct lesions in histology) or AIH (ALT >5xULN; IgG >2xULN or ASMA-positive; lymphocytic piecemeal necrosis in histology) (1). No controlled treatment trials are available for patients with AIH-PBC overlap but both UDCA and corticosteroid therapies seem to be reasonable. Required doses of corticosteroids may be lower in AIH-PBC overlap than in patients with AIH alone.

References


