

# Guidelines for Therapy of Autoimmune Liver Disease

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## ABSTRACT

The principle of therapy for chronic inflammatory liver diseases is the removal of causal agents. For autoimmune liver diseases, however, total removal of causal agents and immune cells is impossible. Therefore, autoimmune liver diseases are presently treated by suppression of the immune response. Autoimmune hepatitis is characteristically responsive to corticosteroids, often used in combination with azathioprine to obtain a steroid-sparing effect. For primary biliary cirrhosis, ursodeoxycholic acid is safe and is the first choice for treatment. Treatment of this autoimmune liver disease should also address various symptoms and complications arising from any associated autoimmune diseases, particularly cholestasis and cirrhosis-related complications. For primary sclerosing cholangitis there are no established immunomodulatory therapies, but medical, endoscopic, and surgical treatments are applicable to this disease. Liver transplantation becomes indicated during the eventual end stages of each of these immune-mediated liver diseases.

**KEYWORDS:** Treatment, guideline, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, overlapping syndrome

Liver damage can be caused by a variety of agents including biological, chemical, and physical factors. Continuous existence of these causal agents leads to the chronic inflammation of the liver after the initial inflammatory and immunological response. Therefore, the therapy for chronic inflammatory liver diseases is removal of these causal agents. For chronic viral hepatitis such as hepatitis B and C, hepatitis viruses should be eliminated by antiviral agents such as nucleoside analogues for hepatitis B virus and interferon for hepatitis C virus. For drug-induced liver injury or alcohol-related liver diseases, cessation

of taking causal agents, namely drugs for drug-induced liver injury or alcohol for alcohol-related liver diseases, is important. For metabolic disorders such as nonalcoholic fatty liver diseases, amelioration of the metabolic condition is important in reducing liver damage.

For autoimmune liver diseases, however, the nature and range of initiating agents are still unknown and, moreover, the immune responses are directed against autoantigens that are impossible to remove. Therefore, autoimmune liver diseases are treated by countering pathogenic immune responses.

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**Table 1 Clinical Stages of Autoimmune Hepatitis and Special Conditions for Treatment**

1. Clinical stages
1) Asymptomatic AIH
2) Symptomatic AIH
3) AIH in remission
4) Relapse during treatment
5) Compensated inactive cirrhosis
6) Decompensated active cirrhosis
7) Liver failure
2. Conditions in which special care is required
1) Children
2) Pregnancy
3) Multiple relapsers or resistant to corticosteroids
4) Concomitance of hepatitis C
5) Variants of AIH
a. AIH-PBC overlap
b. Autoimmune cholangitis
c. AIH-PSC overlap

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

## AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) sometimes arises as an acute but more usually as a chronic hepatitis characterized by autoimmunologic features, generally including a high serum  $\gamma$ -globulin/immunoglobulin G (IgG) concentration and the presence of disease-specific circulating autoantibodies.<sup>1,2</sup> AIH is characteristically responsive to corticosteroid therapy, and the prognosis is good as long as appropriate management is performed.<sup>1,2</sup> The majority of AIH patients show an amelioration of symptoms with anti-inflammatory or immunosuppressive therapy, which is associated with an improvement in serum aminotransferases, bilirubin, and  $\gamma$ -globulin/IgG levels and histological findings. The life expectancy of correctly treated patients can approach that of age- and gender-matched controls.<sup>3</sup> The treatment should be applied according to the clinical stage of the disease (Table 1). The treatment of AIH has three components: (1) specific therapy, namely anti-inflammatory/immunosuppressive therapy; (2) prevention and treatment of corticosteroid side effects; and (3) prevention and treatment of cirrhosis-related complications (Table 2). We discuss therapy in the context of the guidelines promulgated by the American Association for the Study of Liver Diseases (AASLD) for the treatment of AIH.<sup>4</sup> The guidelines are accompanied by a rating, I to IV, based on the weight of the supporting evidence.

### Indications for Treatment

- Treatment should be instituted in patients with serum aminotransferase levels greater than 10-fold the upper limit of normal (Rating, I\*).

**Table 2 Treatment of Autoimmune Hepatitis**

1. Specific therapy: anti-inflammatory/immunosuppressive therapy
1) Induction for remission
2) Maintenance of remission
a. Corticosteroids:predniso(lo)ne
b. Azathioprine
c. UDCA
2. Prevention and treatment of corticosteroids side effects
1) Osteoporosis
2) Infection
3) Diabetes mellitus
4) Gastroduodenal ulcer
5) Mental disturbance
6) Others
3. Prevention and treatment of cirrhosis-related complications
1) Portal hypertension
2) Hepatocellular carcinoma
3) Hepatic failure (jaundice, ascites, encephalopathy)

UDCA, ursodeoxycholic acid.

- Patients with serum aminotransferase levels that are fivefold the upper limit of normal in conjunction with a serum  $\gamma$ -globulin level at least twice the upper limit of normal should be treated (Rating, I).
- Histologic features of bridging necrosis or multiacinar necrosis compel therapy (Rating, I).
- Patients not satisfying the criteria in recommendations in the foregoing three items must be individualized and treatment should be based on clinical judgment. The presence of interface hepatitis without bridging necrosis or multiacinar necrosis on histologic examination does not compel treatment (Rating, III).

Symptomatic AIH should always be treated. However, the choice of drug and dosage should be individualized based on the severity and activity of the disease as judged by symptoms, degree of elevation of serum aminotransferases and  $\gamma$ -globulin/IgG, histological findings, and potential side effects of the drug(s) considered for use.

\* *Comments on the AASLD guideline<sup>4</sup>: for precise explanation refer to the original article (ref. 4).*

*I, evidence from multiple well-designed randomized controlled trials, each involving a number of participants to be of sufficient statistical power.*

*II, evidence from at least one large, well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or from well-designed meta-analysis.*

*III, evidence based on clinical experience, descriptive studies, or reports of expert committees.*

*IV, not rated.*

## Choice of Initial Therapy

- Prednisone, in combination with azathioprine, is the preferred initial treatment because of a lower frequency of side effects (Rating, II).

Corticosteroids are the key drugs used in the anti-inflammatory/immunosuppressive therapy for AIH as shown in the 1960s.<sup>5</sup> Despite the AASLD recommendation, a sufficient dose (0.5 to 1.0 mg/kg body weight) of prednisone (or prednisolone) alone may be sufficient and result in clinical, laboratory, and histological improvement and thus remission of AIH. Azathioprine is usually used in combination with prednisone, as specified in the AASLD recommendation, and is expected to confer a steroid-sparing effect. Although combination therapy of azathioprine with corticosteroid has not been directly compared with corticosteroid alone in large controlled trials with long-term follow-up, there are data that suggest that the combination regimen and corticosteroid-alone regimen have similar efficacy.<sup>5-7</sup> However, considering therapy over the long term, which is virtually lifelong in some patients, supplemental treatment with azathioprine seems wise.<sup>8</sup>

## Goal of Treatment

The primary goal of treatment is clinical remission of symptoms and complete biochemical and histological resolution of inflammation and hepatocellular damage. The ultimate goal is sustained remission without the need for drug therapy (Table 3). Remission can be defined as the resolution of symptoms; normalization of levels of serum aminotransferase, serum bilirubin, and  $\gamma$ -globulin/IgG; and an improvement of liver histology either to normal or to only mild portal hepatitis.<sup>4</sup> Notably, normalization of serum aminotransferase levels does not necessarily indicate histological normalization.<sup>9</sup>

## Induction and Maintenance of Remission

- Conventional treatment regimens should be continued in adults and children until remission, treatment

**Table 3 Goals for the treatment of Autoimmune Hepatitis**

1. Primary end point: normalization of alanine aminotransferase
2. Secondary end point: normalization of the $\gamma$ -globulin and immunoglobulin G levels
3. Tertiary end point: normalization of histological activity
4. Quaternary end point: resolution of fibrosis
5. Final goal: to achieve sustained remission without the need for drug therapy, maintaining the hepatic reserve

failure, incomplete response, or drug toxicity. Once disease remission has been achieved, drug withdrawal should be attempted (Rating, II).

Initial therapy is continued until remission, defined by patients becoming asymptomatic and showing normal laboratory tests except for a less than twofold elevation in serum transaminases, with histological features of minimal or no inflammatory activity. However, the treatment may be stopped if there is treatment failure (see late) or if there is intolerable development of drug adverse effects.

Corticosteroids should be withdrawn gradually over a long period with the prednisone dose being decreased by 5 to 10 mg each week to a dose of 30 mg prednisone per day, followed then by 2.5-mg reduction each week until complete withdrawal.<sup>1,2</sup> A typical maintenance dose of prednisone is less than 10 mg daily, 5 to 10 mg daily, or 10 mg every other day. In patients who have had combination therapy, maintenance therapy with azathioprine alone is desirable.<sup>4</sup> The dose of azathioprine can be increased to 2 mg/kg per day and the dose of prednisone decreased by 2.5 mg each month until complete withdrawal. In patients taking prednisone alone, among whom maintenance therapy with azathioprine alone is desired, azathioprine 2 mg/kg daily can be added after which the dose of prednisone can be reduced by 2.5 mg each month.<sup>4</sup> Ursodeoxycholic acid (UDCA) 10 mg/kg body weight can be also added to reduce the dosage of prednisone until remission is achieved or used even after the complete withdrawal of prednisone.<sup>10</sup>

It is recommended that maintenance therapy be continued for at least 6 months after histological improvement. There has been no consensus, however, about how long such maintenance therapy should be continued. It was shown in one study that the probability of sustained remission without therapy was higher in patients who had received continuous immunosuppressive therapy for 4 years compared with those who had received this for 2 years or less than 2 years (67% versus 17% versus 10%, respectively).<sup>11</sup> Krawitt<sup>1</sup> recommended long-term maintenance therapy for most AIH patients and even lifelong maintenance therapy for adults and children with cirrhosis at the time of the initial biopsy, particularly children with type 2 AIH.

## Assessment of Treatment Effect

The effect of treatment is assessed based on (1) reduction of disease activity as reflected by serum transaminase and bilirubin levels, (2) improvement in liver function as judged by prothrombin time and synthesis of protein as judged by serum albumin, and (3) suppression of the immune response as judged by serum  $\gamma$ -globulin/IgG. The serum autoantibody levels do not

appear to correspond closely to disease activity and need not be used to monitor activity.<sup>1</sup>

The liver biopsy may be a good marker to assess the disease activity in patients receiving maintenance therapy and to decide the timing of the cessation of the maintenance therapy. However, there is no consensus about the frequency with which liver biopsy should be performed. The presence of interface hepatitis strongly predicts relapse after cessation of treatment.<sup>9,12</sup> Drug withdrawal is possible in up to 80% of patients with normal liver histology compared with less than 50% of those with persistent portal or interface hepatitis.<sup>12,13</sup>

### Relapse During or After Achieving Remission

- Relapse is common in adults and children after drug withdrawal, and patients should be monitored for this occurrence by regular determinations of serum aminotransferase, bilirubin, and  $\gamma$ -globulin levels (Rating, II).
- Adults who have relapsed more than once should be treated with combination prednisone and azathioprine therapy, low-dose prednisone, or azathioprine only (Rating, II).

Patients are considered to have relapsed if the serum aminotransferase is increased to more than threefold the upper limit of normal. Relapse usually occurs within the first 15 to 20 months following withdrawal of immunosuppressive therapy,<sup>14</sup> especially among those who had cirrhosis on the initial liver biopsy.<sup>15,16</sup> Patients in relapse should be given the drug at initial induction doses and drug withdrawal should not be attempted again until clinical remission is achieved.

#### THE LIKELIHOOD OF RELAPSE

A relapse can be predicted from the serum IgG levels and histological findings when drug withdrawal is being considered. It was reported that the only variable predictive of relapse after initial treatment was  $\gamma$ -globulin levels because levels were 3.3 and 2.8 g/dL in relapsers versus nonrelapsers, respectively.<sup>17</sup> Relapse among Caucasian patients was also more frequent in those with the human leukocyte antigen phenotype A1, B8, DR3.

### Treatment Failure or Suboptimal Response to Initial Therapy

- High doses of prednisone alone or prednisone in combination with azathioprine should be used in treatment failure (Rating, III).

Approximately 10% of patients have clinical and laboratory deterioration despite compliance with conventional treatment.<sup>6,18</sup> Failure is characterized by sustained

activity, development, or worsening, thus leading to cirrhosis and death or the need for liver transplantation.

The optimal therapy for treatment failure or suboptimal responses to initial therapy is not well established. Treatment with higher doses of standard therapy drugs can achieve clinical remission in up to 70% of such patients within 2 years.<sup>18</sup> A regimen suggested in the AASLD guideline includes either monotherapy with predniso(lo)ne (60 mg daily) or a combination therapy with predniso(lo)ne (30 mg daily) and azathioprine (50 mg daily). This regimen is continued for at least 1 month, after which the dose of predniso(lo)ne is reduced by 10 mg and the dose of azathioprine reduced by 50 mg after each month of clinical improvement. Dose reduction should be continued until conventional maintenance doses have been reached.

Krawitt and Bonis<sup>2</sup> recommended administering azathioprine on an mg per kg basis (2 mg/kg per day up to a maximal dose of 200 mg daily) or 6-mercaptopurine (6-MP)<sup>19</sup> (up to 100 mg daily) in this setting, while increasing predniso(lo)ne to the 40 to 60 mg per day range. In responding patients, they recommended continuing azathioprine or 6-MP for up to 1 year before considering dose reduction, while reducing the dose of predniso(lo)ne. Cyclosporine,<sup>20</sup> tacrolimus,<sup>21</sup> methotrexate,<sup>22</sup> and mycophenolate mofetil<sup>23</sup> have also been tried in a small number of patients and are being used in patients refractory to or intolerant of azathioprine and/or 6-MP. So far, there has been no clear demonstration of efficacy of these alternative therapies for AIH.

### Management of Patients with Special Conditions

#### ASYMPTOMATIC AIH OR AIH WITH MILD ACTIVITY

The outcome is good in patients with AIH who are asymptomatic at presentation, and such patients may not require any immunosuppressive therapy. In a recent report,<sup>24</sup> the 10-year survival rates were similar for symptomatic and asymptomatic groups of patients, 80% and 84%, even though only half of the asymptomatic group received therapy. However, survival was significantly worse in patients who had cirrhosis at baseline, regardless of whether they had symptoms or had received immunosuppressive therapy, and 25% of initially asymptomatic patients ultimately developed symptoms during follow-up. From these results, the authors emphasized the need for regular follow-up in all patients with AIH. There is the opinion, given the serious outcome of AIH in general, that asymptomatic patients with biochemical or histological evidence of activity should be given immunosuppressive treatment.

UDCA is a hydrophilic bile acid with putative immunomodulatory capacities that has beneficial effects in patients with type 1 AIH<sup>10,25</sup>; however, there are no

data on the use of UDCA in the induction or maintenance of remission of AIH.<sup>1,8</sup>

Patients in whom treatment has not been initiated should be monitored carefully. Krawitt and Bonis<sup>1,2</sup> recommended biopsy no longer than 2 years after the diagnosis in such patients to assess evidence of disease progression.

#### SEVERE AIH

- Prednisone in combination with azathioprine or a higher dose of prednisone alone is the appropriate treatment for severe AIH in adults (Rating, I).

Three randomized controlled trials have shown improvement in the clinical and histological features and survival of patients with severe AIH after corticosteroid therapy.<sup>6,7,26</sup> Subsequent studies have indicated that patients with cirrhosis historically respond to corticosteroid treatment as well as do patients without cirrhosis.<sup>27</sup> Furthermore, the 20-year life expectancy for all treated patients exceeds 80%, and the survival rates of such patients resemble those of age- and sex-matched normal subjects from the same geographical region.<sup>27</sup>

#### Inactive Established Cirrhosis

- Treatment may not be indicated in patients with inactive cirrhosis, preexistent comorbid conditions, or drug intolerances (Rating, III).

Patients with inactive cirrhosis characterized by normal or near-normal serum aminotransferase levels and absence of inflammatory cells on liver biopsy may be at increased risk for the development of corticosteroid-related side effects, and the benefits of treatment are uncertain.<sup>1</sup> Therefore, treatment may not be indicated for these conditions.

#### Decompensated Active Cirrhosis

- Corticosteroid therapy should be considered in the decompensated patient (Rating, III).

Treatment should not be withheld from patients with decompensated cirrhosis who have active disease.<sup>1</sup> The response may be excellent even in those who have already experienced bleeding from esophageal varices or who have significant ascites. Most patients respond to treatment, and the 10-year survival rate for treated patients, including those with cirrhosis, exceeds 90%.<sup>3</sup>

The fibrosis accompanying the cirrhotic liver can be reversible.<sup>28,29</sup> In one series of 97 patients, actual reversibility of fibrosis was demonstrated in 8 of 14

patients who had biopsies evaluated both before and after treatment.<sup>28</sup> Although a sampling error could not be excluded, the biopsies were evaluated under code by two pathologists.

#### Liver Transplantation

- Liver transplantation should be considered in the decompensated patient who is unable to undergo or be salvaged by drug therapy (Rating, III).

Patients with or approaching end-stage liver disease, and particularly those refractory to or intolerant of immunosuppressive therapy, require liver transplantation. The outcome in AIH after liver transplantation is good; the 5-year patient and graft survival ranges from 83% to 92% and the 10-year survival is ~75%.<sup>30-32</sup>

#### Follow-up of Patients

##### MONITORING FOR DRUG-RELATED SIDE EFFECTS

- All patients treated with prednisone alone or in combination with azathioprine must be monitored for the development of drug-related side effects (Rating, III).

Side effects require that treatment be discontinued in ~10% of patients.<sup>1</sup> A reasonable approach in this setting is to treat with either corticosteroids or azathioprine alone, whichever is tolerated at a dose that controls disease activity. Azathioprine alone may be considered in patients at increased risk for corticosteroid side effects. However, combination therapy is generally preferable because of the convincing data documenting the efficacy of corticosteroids as an initial treatment.

**Side effects of corticosteroids** Patients can develop severe and potentially debilitating side effects from prolonged use of corticosteroids. These include osteoporosis and vertebral compression, avascular necrosis, type 2 diabetes, cataracts, hypertension, and infections including exacerbation of tuberculosis and psychosis, in addition to the usual "cushingoid" features of facial rounding, acne, dorsal hump formation, and truncal obesity.<sup>6</sup> The most common reasons for treatment withdrawal are intolerable cosmetic changes or obesity (47%), osteopenia with vertebral compression (27%), and brittle diabetes (20%).<sup>33</sup>

The risk of corticosteroid-related side effects is known to increase among patients with diabetes, osteoporosis, emotional instability or a history of psychosis, or poorly controlled hypertension. These conditions are not necessarily contraindications for the use of corticosteroids, but their presence requires special precautions and

**Table 4 Complications of Azathioprine**

- Cholestatic hepatitis
- Veno-occlusive disease
- Pancreatitis
- Nausea
- Emesis
- Rash
- Bone marrow suppression

close monitoring of patients. In addition, they may influence the decision to use azathioprine as part of the initial treatment regimen.<sup>1</sup>

**Side effects of azathioprine** The side effects of azathioprine include cholestatic hepatitis, veno-occlusive disease, pancreatitis, severe nausea, emesis, rash, and bone marrow suppression<sup>4</sup> (Table 4). These side effects develop in fewer than 10% of patients receiving azathioprine at 50 mg daily, and they can be improved by reduction of the dose or discontinuation of the drug. In some patients, azathioprine causes severe nausea and epigastric pain, which may be circumvented by switching to the analog 6-MP. Conditions in which the use of azathioprine is not recommended are preexisting cytopenia, malignancy, thiopurine methyl transferase deficiency, and possibly pregnancy, although teratogenic effects of azathioprine may be trival (Table 5).<sup>34</sup>

#### SCREENING FOR HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is so inconspicuous among patients with AIH that its nonoccurrence is almost a defining marker of the disease; however, the presence of cirrhosis or a coexisting hepatitis B or C would theoretically increase the risk of HCC.<sup>35</sup> Thus, not surprisingly, a survival benefit from screening for HCC among patients with AIH has not been proved. However, AIH patients with cirrhosis are recommended to undergo monitoring for HCC based on  $\alpha$ -fetoprotein levels and ultrasound scan of the liver every 12 months.

#### Patients Who Need Special Care

There are patients for whom special circumstances dictate that the usual therapy be modified in terms of the decision to treat, timing of treatment, and the choice of medications.

#### CHILDREN

- Treatment is warranted in most children at the time of diagnosis (Rating, II).
- Treatment in children should be adjusted to clinical and laboratory findings in an individualized fashion, recognizing that therapy is frequently long term (Rating, III).

**Table 5 Conditions in Which Use of Azathioprine Is Not Recommended**

- Preexisting cytopenia
- Malignancy
- Thiopurine methyltransferase deficiency
- ? Pregnancy

- Azathioprine or 6-MP is preferred as a corticosteroid-sparing agent in children, especially when high doses of prednisone are required for disease control (Rating, III).
- Children who experience treatment failure should be treated with high-dose corticosteroid regimens and considered for liver transplantation (Rating, III).

AIH tends to be more severe in children than adults. One reason for this could be delay in making the diagnosis because up to one half of children with AIH have cirrhosis upon diagnosis,<sup>36,37</sup> but alternatively, cirrhosis may evolve more rapidly in children than in adults. Although corticosteroids are effective in all types of childhood AIH, patients with liver/kidney microsomal antigen 1 (LKM1) have a higher frequency of acute hepatic failure and relapse after corticosteroid withdrawal than patients with antinuclear antibodies (ANAs) or smooth muscle autoantibodies.<sup>38</sup>

Azathioprine or 6-MP is preferred as a corticosteroid-sparing agent in children, especially when high doses of predniso(lo)ne are required for disease control. In children for whom corticosteroids become unacceptable because of side effects, cyclosporine could be an alternative to corticosteroid.<sup>39</sup> Predniso(lo)ne (0.3 to 0.5 mg/day) and azathioprine (1.5 mg/day) can be combined with cyclosporine.

#### Pregnancy

The usual therapy consists of corticosteroids and/or azathioprine, both of which appear safe during pregnancy, and when pregnant women with AIH are treated appropriately, they have successful pregnancies. In the first substantial case series reported, the outcome for the mother and baby was favorable.<sup>40</sup> The authors concluded that in chronic active hepatitis fertility is reduced but pregnancies that occur can proceed without detriment to the mother provided that prednisolone treatment is maintained, that a higher than normal fetal loss can be expected, and that babies may be born prematurely but are normal.<sup>40</sup> Notably, cessation of therapy during pregnancy in such patients has been associated with relapse of the disease.<sup>41,42</sup> Patients need to be monitored carefully during pregnancy and several months postpartum because of the risk of flares in disease activity.<sup>41,42</sup>

Although azathioprine can be used during pregnancy, patients may be concerned about possible risks, but these could be less than effects on the disease related to withdrawal of the drug.

### Concomitance of Hepatitis C

AIH is sometimes accompanied by features of chronic hepatitis C. In this situation, treatment should first be directed toward AIH because type 1 interferons may induce exacerbation of AIH<sup>43</sup> or occurrence of other autoimmune diseases; the use of corticosteroids may result in raising hepatitis C viral loads, but this strategy is safer as an initial approach. For this condition, UDCA may also be effective.<sup>44</sup>

### PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease that predominantly affects middle-aged women. The characteristic pathological lesion is nonsuppurative destruction of interlobular bile ducts associated with granulomata in portal tracts. The interlobular bile duct lesion leads to progressive ductopenia followed by slowly progressive cholestasis, fibrosis, cirrhosis, and eventually liver failure.<sup>45,46</sup>

The disease is basically autoimmune in nature, although initiating factors are unknown.<sup>47,48</sup> Epidemiologic data indicate a variable incidence and prevalence of the disease among populations, and several genetic factors have been identified as determinants of disease susceptibility or progression.<sup>49</sup> Antimitochondrial antibodies (AMAs) are unique among autoimmune serologic reactants because of their extremely high association with the index disease PBC. This autoantibody response is specifically directed only to the lipoyl domain of the mitochondrial 2-oxo-acid dehydrogenase complexes. Various environmental factors, including molecular mimicry by either microorganisms or xenobiotics, have also been proposed. Rieger et al<sup>50</sup> searched for environmental mimotopes in the form of xenobiotics and identified 2-octynoic acid as a high-affinity reactant for AMA. A hypothesis gaining support is that environmental factors may trigger disease in genetically predisposed individuals.

The clinical stages of PBC consist of asymptomatic, symptomatic, cirrhotic, and hepatic failure (Table 6). Appropriate treatment should be given according to the clinical stage of the disease and has two components. These are (1) specific therapy, meaning suppression of the underlying pathogenic process, and (2) management of symptoms and complications resulting from either associated autoimmune diseases, chronic cholestasis, or cirrhosis (Table 7). AASLD has provided guidelines for the treatment of PBC.<sup>51</sup>

**Table 6 Clinical Stages of Primary Biliary Cirrhosis**

- |   |
|---|
| 1. Clinical stages                              |
| 1) Asymptomatic stage                           |
| 2) Symptomatic stage                            |
| 3) Cirrhotic stage                              |
| 4) Liver failure                                |
| 2. Conditions in which special cares are needed |
| 1) Pregnancy                                    |
| 2) Variants of PBC                              |
| a. AIH-PBC overlap syndrome                     |
| b. Autoimmune cholangitis                       |

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis.

### Specific Therapy: Suppression of Underlying Pathogenic Process

- Appropriately selected patients with PBC with abnormal liver biochemistry should be advised to take UDCA, 13 to 15 mg/kg daily, either divided doses or as a single daily dose. If cholestyramine is used, 4 hours should elapse between cholestyramine intake and UDCA administration (I A, D, and E\*).

### URSODEOXYCHOLIC ACID

UDCA is now the first choice for drug therapy for PBC. An analysis of data from 548 patients collected from three large randomized trials shows that UDCA therapy leads to a significant increase in survival after up to 4 years of therapy.<sup>52-55</sup> A recent study also showed that the UDCA treatment was associated with a marked improvement in serum biochemical markers of cholestasis, that is, alkaline phosphatase,  $\gamma$ -glutamyltransferase, and bilirubin. Furthermore, this biochemical response was associated with a survival similar to that of the matched control population, clearly supporting the favorable effects of this treatment in PBC.<sup>56</sup> The treatment does not seem to reduce the symptoms but adverse effects of UDCA are very rare, the most common being gastrointestinal symptoms such as stomach ache and diarrhea.

Fibrate bezafibrate, a fibric acid derivative used to treat hypercholesterolemia,<sup>57-59</sup> and fenofibrate<sup>60</sup> have also been shown to confer biochemical improvement. These drugs can be given alone, but a combination with

*\*Comments on the AASLD guideline<sup>51</sup>:*

*Categories reflecting the evidence to support the use of a guideline recommendation (category and definition):*

*A, Survival benefit; B, improved diagnosis; C, improvement in quality of life; D, relevant pathophysiologic parameters improved; E, impacts, cost of health care.*

*These standardized guidelines of the practice guideline of the AASLD have been modified from the categories of the Infectious Diseases Society of America's quality standards (cited from ref. 50). For precise explanation, refer to the original article (ref. 51).*

**Table 7 Treatment of Primary Biliary Cirrhosis**

1. Specific therapy: suppression of underlying pathogenic process
  - 1) Ursodeoxycholic acid (UDCA)
  - 2) Fibrate
2. Management of symptoms and complications
  - 1) Symptoms and complications resulting from associated autoimmune diseases
    - a. Sicca syndrome and Sjögren's disease
    - b. Thyroid disease
    - c. Rheumatoid arthritis
    - d. Others
  - 2) Symptoms and complications resulting from cholestasis
    - a. Pruritus
    - b. Osteoporosis
    - c. Fat-soluble vitamin deficiency
    - d. Hypercholesterolemia and xanthomas
    - e. Malabsorption
  - 3) Symptoms and complications resulting from cirrhosis
    - a. Portal hypertension
    - b. Hepatocellular carcinoma
3. Liver transplantation

UDCA is recommended because the mechanism of action is different.

#### IMMUNOSUPPRESSIVE DRUGS

At present, there are insufficient data to support the use of immunosuppressive therapy for PBC, although considerable work remains to be done.<sup>51</sup>

Asymptomatic PBC may be followed without any medications for ~3- to 4-month intervals. However, when the serum biliary enzyme levels begin to increase, it is recommended to administer 13 to 15 mg/kg daily of UDCA based on the AASLD recommendation.

#### Management of Symptoms and Complications

Symptoms and complications that require therapy arise in several categories (Table 7), including those resulting from chronic cholestasis, associated autoimmune diseases, and cirrhosis. Associated autoimmune diseases, such as the Sicca syndrome and Sjögren's disease, Hashimoto's thyroiditis, and rheumatoid arthritis are frequently seen.<sup>61</sup>

#### COMPLICATIONS RESULTING FROM ASSOCIATED AUTOIMMUNE DISEASES

##### Sicca Syndrome and Sjögren's Disease

###### AASLD RECOMMENDATION<sup>51</sup>

- All patients should be asked directly about dry eyes, dry mouth, dysphagia, and a dry vagina in women

because patients often do not volunteer these symptoms (III C).

- If symptoms are present, appropriate therapy should be offered.

Eyes (xerophthalmia include corneal ulceration), mouth (xerostomia), esophagus, and vagina are involved in complications of PBC and result from decreased secretion in these tissues or organs. Symptoms caused by the Sicca syndrome should be treated as appropriate.

#### Thyroid Diseases

###### AASLD RECOMMENDATION<sup>51</sup>

- Serum thyroid-stimulating hormone (TSH) should be checked at diagnosis of PBC and periodically thereafter (III C).

Thyroid disease including Hashimoto's thyroiditis affects 15% to 25% of PBC patients.<sup>62</sup> Hypothyroidism is treated with thyroid hormone replacement in a dose that keeps TSH levels in the normal range.

#### COMPLICATIONS RESULTING FROM CHOLESTASIS

###### AASLD Recommendations<sup>51</sup>

##### PRURITUS

- Cholestyramine is the drug of first choice (III C).
- In patients who fail the treatment or are intolerant to the side effects of cholestyramine, rifampicin should be used as a second-line therapy (III C).
- Opioid antagonists can be considered in resistant cases (III C).
- Liver transplantation is indicated for uncontrollable pruritus (IV).

##### OSTEOPOROSIS

- Bone mineral density should be assessed with dual x-ray absorptiometry when the diagnosis of PBC is first made and every 2 years thereafter.
- Education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation) and vitamin D and calcium supplementation should be given (III C).
- Hormone replacement therapy, best by the transdermal route, is recommended where appropriate (III C).
- If osteoporosis is evident, therapy with a bisphosphonate is advised (III D).

**FAT-SOLUBLE VITAMIN DEFICIENCY**

- In patients with hyperbilirubinemia, fat-soluble vitamin replacement is probably best given using the water-soluble form of the fat-soluble vitamins (III C).

**COMPLICATIONS RESULTING FROM CIRRHOSIS****Portal Hypertension****AASLD RECOMMENDATIONS<sup>51</sup>**

- PBC patients should be screened for the presence of varices when first diagnosed and every 3 years until found (III B, C).
- If and when varices are found, standard prophylactic measures should be taken.

**Hepatocellular Carcinoma**

HCC develops predominantly in older male patients with advanced-stage PBC.<sup>63</sup> The disease-specific annual mortality rate for PBC is estimated to be 0.008 for women and 0.028 for men.<sup>63</sup> However, HCC does not affect patients' survival.<sup>63-65</sup> In one study, the overall incidence of HCC in a sample of 273 PBC patients with stage III/IV disease was found to be 5.9% (4.1% in women but 20% in men).<sup>64</sup> PBC patients in advanced stages should undergo monitoring for HCC based on the  $\alpha$ -fetoprotein levels and an ultrasound study every 6 to 12 months.

**MANAGEMENT OF LIVER FAILURE****Liver transplantation****AASLD RECOMMENDATION<sup>51</sup>**

- Liver transplantation in PBC is recommended for liver failure (II A, C, D).
- Liver transplantation may be recommended in appropriately selected patients for (1) uncontrollable pruritus (IV C) and (2) severe osteoporosis (IV C).

PBC in advanced stages is a common indication for transplantation.<sup>66</sup> PBC recurs in the allograft, but it is a rare event and does not change the outcome for the patient who has received a transplanted liver.<sup>67,68</sup>

**Timing of liver transplantation** The most reliable determinants of outcome in PBC are the serum bilirubin level and the Mayo risk score.<sup>51,69</sup> Kim et al<sup>70</sup> have

reassessed the Mayo risk score, taking into consideration other factors found to be important in the timing of transplantation in patients with PBC.

**TREATMENT OF PRIMARY BILIARY CIRRHOSIS IN SPECIAL CONDITIONS****Pregnancy****AASLD RECOMMENDATIONS<sup>51</sup>**

- It is currently recommended that any specific therapy (e.g., UDCA) be withheld in women with PBC contemplating pregnancy because its safety during the first trimester has not been proved. UDCA therapy during the last trimester of pregnancy appears to be safe and may be beneficial in mothers with cholestasis (III C, D).
- Patients who are pregnant should undergo an esophagogastroduodenoscopy to check for varices and given nonselective  $\beta$ -blocker therapy if varices are found. The obstetrician should be advised to minimize the duration of the second stage of labor (III C).

**TYPES OF CLINICAL PROGRESSION AND PREDICTION OF PROGNOSIS**

Although most patients with PBC have a good outcome, a number do progress to liver failure and need liver transplantation. Therefore, it is important to predict outcome and, if possible, to intervene with treatment. One of the antinuclear protein antibodies, anti-gp210, has become a good prospect for predicting outcome of PBC.<sup>71,72</sup> Nakamura et al<sup>72</sup> studied the progression of PBC when associated with ANA positivity, using stepwise Cox proportional hazard regression and an unconditional stepwise logistic regression model, based on data from 276 biopsy-proven cases. With death due to hepatic failure/liver transplantation defined as the end point, significant risk factors at the time of initial liver biopsy were positive anti-gp210 antibodies, late stage of disease (Scheuer's stage 3, 4), and male sex. When clinical progression to death due to hepatic failure/liver transplantation (i.e., hepatic failure type progression) or to the development of esophageal varices or HCC without developing jaundice (total bilirubin  $<1.5\text{mg/dL}$ ) (i.e., portal hypertension type progression) was defined as an end point for PBC patients in the early stage (Scheuer's stage 1, 2), positivity for anti-gp210 was a significant risk factor for hepatic failure type progression, whereas antitromer positivity was a significant risk factor for portal hypertension type progression. Their results indicate that there are two different progression types in PBC: the hepatic failure type and the portal hypertension

type, reflected by positivity for anti-gp210 and anti-centromere, respectively.

### VARIANTS OF AUTOIMMUNE HEPATITIS OR PRIMARY BILIARY CIRRHOSIS

A proportion of patients (~5% to 10%) with PBC or primary sclerosing cholangitis (PSC) have clinical and serologic features suggesting the presence of AIH. Conversely, some patients with AIH have findings compatible with PBC or PSC, and there are also patients in whom clinical features lie at the borderline between these diseases. In a report from Mayo Clinic, 225 patients with either type I AIH, PBC, or PSC (162, 37, and 26 patients, respectively) defined by standard criteria, were analyzed for serologic and clinical features suggesting variant forms of AIH.<sup>73</sup> Among these 225 patients, 18% had diseases with overlapping features including 7% with AIH/PBC, 6% with AIH/PSC, and 11% with AIH/autoimmune cholangitis (AIC). Nomenclature and diagnostic criteria for these variant forms of AIH have not yet been standardized. Despite these difficulties and the lack of a well-established “gold standard” marker, these overlaps have become widely recognized and reported.<sup>74–76</sup>

#### AIH-PBC Overlapping Syndrome and Autoimmune Cholangitis

Overlapping cases of AIH-PBC generally fall into two categories. One is that of patients with histological features characteristic of AIH but serologic findings typical of PBC (i.e., AMA-positive AIH).<sup>76</sup> The clinical course and response to therapy appear to be almost identical to that seen in type 1 AIH. On the other hand, patients may have histological features suggesting PBC but are often seronegative for AMA and generally have circulating ANAs and/or smooth muscle antibodies. This condition has been referred to as autoimmune cholangiopathy, immune cholangitis, or AIC<sup>52,78,79</sup> and is considered as a variant form of PBC.<sup>79</sup>

#### TREATMENT

Patients who have AMA-positive AIH-PBC overlap usually respond to corticosteroids, and the treatment should be started with corticosteroids as for patients with classic type 1 AIH.<sup>80</sup> After remission is achieved, the patient can be maintained with 600 to 900 mg UDCA daily.<sup>81</sup>

Patients with autoimmune cholangitis (AMA-negative PBC) are also responsive to corticosteroids when serum aminotransferase levels are high. After remission is achieved, this condition can also be maintained with UDCA.

### PRIMARY SCLEROSING CHOLANGITIS

PSC is a chronic progressive disorder of unknown etiology that is characterized by inflammation, fibrosis, and stricturing of medium to large intrahepatic and extrahepatic bile ducts. The majority of Caucasian cases are complicated by underlying ulcerative colitis.<sup>82</sup> PSC is associated with numerous complications including cholestasis and associated problems resulting from stricture formation, cholelithiasis, cholangitis, and cholangiocarcinoma.<sup>82</sup> In addition, PSC may follow a progressive course resulting in portal hypertension and liver failure.

The goals of treatment in PSC are (1) retardation and reversal of the disease process; (2) controlling symptoms induced by complications of PSC, mainly induced by cholestasis; and (3) the management of advanced liver disease and its complications. The therapy of PSC is, however, unsatisfactory. Standard doses of UDCA lead to improvements in biochemical abnormalities but not in histology, cholangiographic appearances, or survival. Several innovative therapies have been tried in PSC but with scant evidence of benefit.<sup>82</sup> For patients with high-grade strictures, endoscopic dilatation is beneficial. Liver transplantation is successful for end-stage liver disease related to PSC and improves survival.<sup>82</sup> PSC may recur after transplantation but is rarely progressive. The most dreaded complication of PSC is cholangiocarcinoma.

#### AIH-PSC Overlap

AIH-PSC overlap syndrome is a relatively uncommon variant of PSC. Corticosteroids alone are unlikely to result in clinical, biochemical, and histological remission. Patients with AIH/PSC overlap syndrome seem to benefit from immunosuppression plus UDCA therapy, survival being apparently better than in “classical” PSC.<sup>84</sup> The development of superimposed AIH on PSC could not be predicted from baseline characteristics and initial response to UDCA therapy.

### CONCLUSIONS

Autoimmune diseases of the liver in earlier times cast a dismal prospect by reason of relentless progression to liver failure; current therapies have greatly changed this perspective. Wisely used immunomodulation has resulted in AIH becoming a therapeutically tractable disease, and the empirically introduced UDCA has substantially ameliorated the course and outcome of PBC. Unfortunately, PSC is yet to come under therapeutic control. In the future, novel immunobiologic reagents may well bring further benefits for patients with these diseases.

### ABBREVIATIONS

AASLD American Association for the Study of Liver Diseases

AIC	autoimmune cholangitis
AIH	autoimmune hepatitis
AMA	antimitochondrial antibody
ANA	antinuclear antibody
HCC	hepatocellular carcinoma
IgG	immunoglobulin G
LKM1	liver/kidney microsomal antigen 1
6-MP	6-mercaptopurine
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid

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