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Current Status of Autoimmune Hepatitis in Japan

Yasuhiro Miyake* Kazuhide Yamamoto†

*Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, miyake43@md.okayama-u.ac.jp

†Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

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Yasuhiro Miyake and Kazuhide Yamamoto

Abstract

Autoimmune hepatitis (AIH) is a chronic and progressive disease characterized by histological interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies. Multiple factors, including molecular mimicry, a genetic background including major histocompatibility complex class II, and defective function of regulatory T-cells, are involved in the pathogenesis. The diagnosis is made based on the scoring system of the International Autoimmune Hepatitis Group, the sensitivity and specificity of which are90%, respectively. AIH is classified into 3 sub-types based on the profiles of circulating autoantibodies: anti-nuclear antibody and/or smooth muscle antibody-positive (type 1), anti-liver-kidney microsomal antibody-positive (type 2), and anti-soluble liver antigen/liver-pancreas antigen antibody- positive (type 3). Recently, however, the number of atypical cases lacking the usual features has increased-for example, patients with acute-onset or fulminant-type AIH, autoantibody-negative patients, male patients, and patients with bile duct injury-and thus the clinical features of AIH have been diversified. AIH is responsive to immunosuppressive treatment in most cases; however, relapse occurs in more than 80% of patients within 1 year after immunosuppressive treatment withdrawal. The 10-year survival rate and the 10-year hepatocellular carcinoma-free rate are90%, respectively, indicating that some patients reach liver failure or develop hepatocellular carcinoma. To improve the prognosis of these patients, persistent normalization of transaminase is required.

KEYWORDS: autoimmune hepatitis, epidemiology, pathogenesis, diagnosis, prognosis

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Review

Current Status of Autoimmune Hepatitis in Japan

Yasuhiro Miyake*, and Kazuhide Yamamoto

Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan

Autoimmune hepatitis (AIH) is a chronic and progressive disease characterized by histological interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies. Multiple factors, including molecular mimicry, a genetic background including major histocompatibility complex class II, and defective function of regulatory T-cells, are involved in the pathogenesis. The diagnosis is made based on the scoring system of the International Autoimmune Hepatitis Group, the sensitivity and specificity of which are > 90%, respectively. AIH is classified into 3 sub-types based on the profiles of circulating autoantibodies: anti-nuclear antibody and/or smooth muscle antibody-positive (type 1), anti-liver-kidney microsomal antibody-positive (type 2), and anti-soluble liver antigen/liver-pancreas antigen antibody-positive (type 3). Recently, however, the number of atypical cases lacking the usual features has increased—for example, patients with acute-onset or fulminant-type AIH, autoantibody-negative patients, male patients, and patients with bile duct injury—and thus the clinical features of AIH have been diversified. AIH is responsive to immunosuppressive treatment in most cases; however, relapse occurs in more than 80% of patients within 1 year after immunosuppressive treatment withdrawal. The 10-year survival rate and the 10-year hepatocellular carcinoma-free rate are > 90%, respectively, indicating that some patients reach liver failure or develop hepatocellular carcinoma. To improve the prognosis of these patients, persistent normalization of transaminase is required.

Key words: autoimmune hepatitis, epidemiology, pathogenesis, diagnosis, prognosis

Autoimmune hepatitis (AIH), first reported by Waldenström in 1950 [1], is a chronic and progressive disease characterized by histological interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies [2]. The prognosis of AIH is generally good with immunosuppressive treatment, but some patients may develop hepatocellular carcinoma (HCC) or liver failure [3, 4].

There has been considerable uncertainty about the diagnostic criteria for AIH since identification of the hepatitis C virus (HCV) in 1989 [5]. Anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), and anti-liver-kidney microsomal type 1 antibody (LKM-1), which are important factors for the diagnosis of AIH, are found in 9%, 20%, and 6% of chronic hepatitis C (CHC) cases, respectively, and the overall prevalence of autoantibodies is 30% [6]. Furthermore, CHC patients with autoantibodies have more severe portal-periportal necroinflammation than those without autoantibodies [6]. To establish diagnostic criteria for AIH, a scoring system was proposed by the International Autoimmune Hepatitis

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*Corresponding author. Phone: +81–86–235–7219; Fax: +81–86–225–5991
E-mail: miyake43@md.okayama-u.ac.jp (Y. Miyake)

Group (IAHG) in 1993 [7]. The sensitivity of this scoring system was more than 90%, while the specificity was insufficient, especially in patients with primary sclerosing cholangitis (PSC) [8], so the scoring system was modified in 1999 [8].

Recently, atypical cases lacking the usual features of AIH has also been reported [9–12], with the result that the clinical features of AIH have been diversified. Herein, we review the current status of autoimmune hepatitis.

Pathogenesis

A mechanism of molecular mimicry between foreign and self-antigens is considered to be one of the major sources of pathogenesis in AIH. Several drugs (infliximab, minocycline, atorvastatin, hepatitis A vaccine) and viruses (hepatitis A virus, hepatitis B virus, HCV, Epstein-Barr virus) have been reported as possible triggers for AIH [13–20]. In the molecular mimicry theory, self-reactive T cells, initially activated by infectious pathogens, subsequently provoke a self-destructive response in an organ expressing a cross-reactive self-Ag. For example, in patients with HCV infection, molecular mimicry at the B cell level has been shown between CYP2D6, which is an enzyme targeted by LKM-1 autoantibodies, and the HCV NS3 and NS5a proteins [21]. On the other hand, the development of AIH is associated with genetic background in patients with acute infection of hepatitis A virus and Epstein-Barr virus [20, 22]. Defective suppressor-inducer T cell function may provoke helper T cell activation and antibody production against asialoglycoprotein receptors (ASGPR) and thereby leading to the development of AIH type 1.

Genetic background is an important factor, and individuals with certain major histocompatibility complex (MHC) class II alleles are susceptible to AIH, as in other autoimmune diseases. MHC class II plays an important role in antigen presentation, because peptide antigens are recognized by CD4 T cells in association with MHC class II and types of peptides are determined by the amino acid sequence in the groove of MHC class II. After exposure to foreign antigens, individuals with a certain MHC class II present specific peptides showing molecular mimicry to self antigens, and this may trigger an autoimmune reaction against self antigens. For example, certain amino acid residues of human leukocyte antigen (HLA)-DRβ molecules (Lys71 in Caucasian patients with DRB1*0301 and DRB1*0401 and Arg71 in Japanese patients with DRB1*0405) have been reported to contribute to the susceptibility to AIH [23, 24]. This residue 71 of the DRβ molecule, which is located on top of the α-helix pointing into the peptide-binding groove, may influence peptide binding, orientation, and interaction with the T cell receptor. However, the types of self antigens presented by MHC class II in AIH type 1 have not been clarified.

It has recently been postulated that $CD4^+$ $CD25^+$ regulatory T cells play a role in the pathogenesis of AIH. $CD4^+$ $CD25^+$ regulatory T cells maintain immunological tolerance and suppress autoreactive immune responses. A genetic or acquired defective function of regulatory T cells may cause excessive autoimmune reactions. In patients with AIH, $CD4^+$ $CD25^+$ regulatory T cells are numerically and functionally defective, and the percentage of $CD8^+$ T cells spontaneously undergoing apoptosis is lower than in normal controls [25, 26]. Furthermore, in patients with AIH, Foxp3 expression in $CD4^+$ $CD25^+$ regulatory T cells is lower than in normal controls. Circulating $CD4^+$ $CD25^+$ regulatory T cells increase during early pregnancy, peaking during the second trimester and decreasing postpartum [27]. In contrast, the activity of AIH declines during early pregnancy and flares after delivery [28]. The inverse correlation between $CD4^+$ $CD25^+$ T cells and clinical activity may support the hypothesis that activation of autoreactive $CD8^+$ T cells under the condition of defective $CD4^+$ $CD25^+$ regulatory T cells may play a role in the pathogenesis of AIH.

Diagnosis

In Japan, AIH has been diagnosed based on the criteria proposed by the Intractable Hepatitis Study Group of the Ministry of Health and Welfare of Japan (Japanese criteria) (Table 1) [29]. The criteria consist of hypergammaglobulinemia (or IgG concentration ≥ 2.5 g/dL), circulating autoantibody (ANA- and/or SMA-positive), histological features (plasma cell infiltration, interface hepatitis, and hepatocyte necrosis), and exclusion of other known causes of chronic hepatitis (viruses, alcohol, drugs, Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, *etc.*).

Recently, a revised IAHG scoring system was proposed as a useful diagnostic tool in clinical practice (Table 2) [8]. Papamichalis *et al.* [30] applied the scoring system to 423 patients with liver diseases excluding AIH and reported that the specificity was 98%. In another study applying the scoring system to PSC patients, the specificity was 93% [31]. Omagari *et al.* [32] applied the scoring system to 89 patients who fulfilled the Japanese criteria and reported that the sensitivity was 91%. The scoring system was also reported to be useful for pediatric patients with AIH [33].

The revised IAHG scoring system thus seems to be sufficiently accurate for the diagnosis of AIH, but there have been some difficulties in applying it to atypical forms of diseases. Farias *et al.* [34] reported that only 28% of patients with antimitochondrial antibody (AMA)-positive AIH had scores high enough for a definite diagnosis. On the other hand, Yatsuji *et al.* [35] reported that, in female patients with nonalcoholic fatty liver disease, 97% had a score of 10 or more without including the liver biopsy results. Furthermore, Hayashi *et al.* [36] reported that in the general Japanese population, the rates of ANA-positive samples at 1: 40 and 1: 160 dilutions were 26% and 10%, respectively, with females having a significantly higher positive rate than males. These findings indicate that low titers of ANA may not be sufficiently specific for a diagnosis of AIH, and thus AIH diagnosis requires a liver biopsy.

Patients with AIH are classified into 3 sub-types based on profiles of circulating autoantibodies. AIH type 1 is a classical type, so-called lupoid hepatitis. It is associated with ANA and/or SMA. In Japanese, it is dominantly associated with HLA-DRB1*0405; however, DRB1*0405 does not influence the clinical features [37]. In Caucasians, AIH type 1 is primarily associated with DRB1*0301 and secondarily with DRB1*0401 [38]. Patients with DRB1*0301 differ from those with DRB1*0401 in that they are younger and fail treatment more commonly [39]. On the other hand, DRB1*0401 is associated with a

Table 1 Criteria for diagnosis of autoimmune hepatitis in Japan. The Study Group of the Japanese Ministry of Health and Welfare (29).

General concept

Increased prevalence in younger females, chronic active hepatitis with potential progression to cirrhosis, existence of autoimmune mechanisms in etiology, exclusion of all other known specific causes of chronic hepatitis, such as viruses, alcohol, drugs, etc. good response to corticosteroid therapy (typical).

I. Major findings

1. Persistent elevation of serum aminotransferases
2. Hypergammaglobulinemia of 2.5 g/dL or greater (or IgG concentration of 2.5 g/dL or greater)
3. Circulating autoantibody: a) and/or b)
   a) LE test-positive
   b) ANA (antinuclear antibody)-positive and/or LE test-positive
4. IgM anti-HAV (hepatitis A virus)-negative and absence of other evidence of HBV infection (HBs antigen-negative, anti-HBc antibody-negative or at low titers)
5. Absence of true-positive anti-HCV antibody or other evidence of HCV infection

II. Minor findings

1. Systemic manifestations such as fever, arthralgia, and skin eruption
2. Complications of other autoimmune diseases including collagen disease
3. a) and/or b)
   a) Accelerated ESR (erythrocyte sedimentation rate) at 30 mm/h or faster
   b) C-reactive protein (CRP)-positive

III. Histology

Chronic active hepatitis or cirrhosis with marked plasma cell infiltration and hepatocyte necrosis, absence of features of other specific diagnosis such as α-1-antitrypsin deficiency

Diagnosis of autoimmune hepatitis

1) Diagnostic: Fulfill all criteria of I and III
2) Suggestive: Fulfill all criteria of I and at least one of II
3) Possible: Fulfill all criteria of I

Table 2 Revised scoring system for autoimmune hepatitis. International Autoimmune Hepatitis Group (8).

Parameters/Features	Score
Female sex	+2
ALP: AST (or ALT) ratio:	
< 1.5	+2
1.5–3.0	0
> 3.0	−2
ANA, SMA or LKM-1	
> 1: 80	+3
1: 80	+2
1: 40	+1
< 1: 40	0
AMA-positive	−4
Hepatitis viral markers:	
Positive	−3
Negative	+3
Drug history:	
Positive	−4
Negative	+1
Average alcohol intake	
< 25 g/day	+2
> 60 g/day	−2
Liver histology:	
Interface hepatitis	+3
Predominantly lymphoplasmacytic infiltrate	+1
Rosetting of liver cells	+1
None of the above	−5
Biliary changes	−3
Other changes	−3
Other autoimmune disease	+2
Optional additional parameters:	
Seropositive for other defined autoantibodies (perinuclear staining antineutrophil cytoplasmic antibody, anti-liver specific cytosolic antigen, anti-soluble liver antigen, anti-hepatic asialoglycoprotein receptor, anti-liver-pancreas antigen, and anti-sulfatide)	+2
HLA DR3 or DR4	+1
Response to therapy:	
Complete	+2
Relapse	+3
Interpretation of aggregate scores:	
Pre-treatment:	
Definite AIH	> 15
Probable AIH	10–15
Post-treatment	
Definite AIH	> 17
Probable AIH	12–17

lower frequency of death from liver failure or the need for transplantation.

AIH type 2 is characterized by LKM-1 autoantibodies and/or anti-liver cytosol antibody type 1 (LC1) [40]. The serum LC1 concentration, at variance with that of LKM-1, parallels liver disease activity [41]. Recently, the HLA-DQB1*0201 allele was reported to be the primary genetic determinant of susceptibility to AIH type 2 [42]. The onset resembles acute viral hepatitis with marked elevation of transaminase and hypergammaglobulinemia [40]. Patients with AIH type 2 require prolonged treatment with corticosteroids and immunosuppressants.

AIH type 3 is characterized by the presence of antibody to soluble liver antigen/liver-pancreas antigen (SLA/LP) [43]. Patients with AIH type 3 tend to have lower levels of transaminase, gamma globulin, and bilirubin in comparison to patients with AIH type 1 [44]. Response to immunosuppressive therapy is excellent, but relapses occur frequently.

Atypical Forms of AIH

AIH predominantly affects women, and the clinical characteristics are different between females and males. Among Caucasian patients, the male patients are distinguished from the females by lower frequencies of concurrent autoimmune disease (17% vs. 34%) and HLA DR4 (24% vs. 49%) [45]. Treatment failure occurs more frequently in male patients only if they have HLA DR3. Furthermore, male patients experience relapse more frequently. Among Japanese patients, compared with females, males have a lower frequency of definite diagnosis according to the revised scoring system and lower serum levels of immunoglobulin G [10]. However, Japanese male and female AIH patients are similar in age, form of clinical onset, symptomatic concurrent autoimmune disease, and HLA-DR status. The response to corticosteroid treatment is better in female patients than in males.

Recently, reports on acute onset of AIH have increased, and 26% of Japanese patients have been reported to show acute onset [9]. Patients with acute onset have lower serum levels of albumin, gamma globulin, and immunoglobulin G, and higher serum levels of total bilirubin, AST, and ALT, and more frequently show moderate to severe lobular hepatitis; however, acute onset reflects not only acute AIH but also acute exacerbation of pre-existing chronic disease. On the other hand, patients with acute liver failure have been reported occasionally.

Corticosteroid treatment is of little benefit to patients with acute liver failure, and most of them require liver transplantation [46]. However, low titer autoantibodies are frequently detected in cases of acute liver failure, and the diagnosis of acute liver failure due to autoimmune hepatitis should be made carefully [47].

Bile duct injury, which is characteristic of primary biliary cirrhosis (PBC), is an important condition to consider in patients with AIH. There has been one report of a patient with chronic nonsuppurative destructive cholangitis-like bile duct injuries who did not respond to ursodeoxycholic acid (UDCA) but did respond to prednisolone [48]. In one study, bile duct injury was present in 24% of patients negative for AMA, and 7% had destructive cholangitis [12]. There are no differences in clinical characteristics, including response to immunosuppressive treatment, between patients with and without bile duct injury. Furthermore, there is no difference in the concurrence of inflammatory bowel disease. Recently, 10% of AIH patients have been reported to have magnetic resonance cholangiography findings consistent with PSC [49]. It has been controversial whether these bile duct injuries are histological features of AIH or those of an overlap of AIH and PBC or PSC.

Clinical Features of Japanese AIH

In recent reports from Japan, approximately 10% of AIH patients were male, and the peak incidence was between ages 50 and 60 years in both male and female patients. Approximately 95% of cases were positive for ANA and/or SMA [29, 50]. In a histological analysis, 85% of patients showed interface hepatitis, and rosetting of liver cells was seen in 28% of cases [9]. In the same histological analysis, zone III necrosis was seen in 29% of cases, and acute hepatitis and cirrhosis were diagnosed in 6% and 10% of patients, respectively, at presentation [9]. Concurrent autoimmune diseases (autoimmune thyroiditis, Graves' disease, Sjögren's syndrome, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, rheumatoid arthritis, autoimmune hemolytic anemia, *etc.*) were found in 24% of AIH patients [9]. Positivity for HLA-DR4 was seen in 75% of cases, and there were no patients with DR3 [29]. In other studies, patients negative for DR4 were mainly positive for DR2; however, the frequency of DR2 was similar between patients with AIH and healthy controls [37, 51]. These studies also demonstrated that the proportion of patients with DR4 was low among patients aged < 30 years. Interestingly, concurrence of thyroid disease (autoimmune thyroiditis, Graves' disease) is reported to be associated with DR4 [51]. There are some notable differences in clinical features between Japanese and Caucasian patients with AIH (Table 3). In Japanese patients compared with Caucasian patients, proportions of patients aged < 40 years, male patients, and patients with histological cirrhosis are smaller [29, 52–55]. In Caucasian patients, those with HLA DR3 and DR4 are independently susceptible to autoimmune hepatitis [56], while DR4 is predominant in Japanese patients and there are no Japanese patients with DR3 [29]. Patients with DR3 have an earlier age of onset, and they deteriorate during corticosteroid treatment, die of liver failure, and require liver transplantation more often than those with DR4 [39, 57]. Female patients have DR4 more frequently than do males

Table 3 Comparison of clinical features between Japanese patients and Caucasian patients with AIH type 1 (8, 10, 29, 45, 50–52, 79–81).

	Japanese patients	Caucasian patients
Peak age at presentation	50–70	40–70
Male patients (%)	12–13	21–22
ANA positive (%)	84–95	72–79
SMA positive (%)	64	69–75
ANA and/or SMA positive (%)	95–99	97
Main HLA-DR (%)	DR4 (70–75)	DR3 (51–57), DR4 (43–49)
Concurrent autoimmune disease (%)	24	30–31
Autoimmune thyroiditis (%)	11	13–15
Cirrhosis at presentation (%)	10–12	27–34

[45]. On the other hand, patients with DR4 are older and respond better to corticosteroid treatment. The differences in clinical features are considered to be due to the HLA-DR status.

Treatment

In the practice guidelines of the American Association for the Study of Liver Diseases, patients with serum AST levels ≥ 10-fold the upper limit of normal or with serum AST ≥ 5-fold the upper limit of normal in conjunction with a serum gamma globulin level at least twice the upper limit of normal are recommended for immunosuppressive treatment [58]. However, to improve their prognosis, persistent normalization of transaminase is required [3, 4]. Thus, patients with abnormal levels of transaminase should receive some treatments.

In a study of Japanese patients, normalization of ALT at 6 months after the introduction of initial treatment was achieved in 89% of patients treated with corticosteroid, 100% of patients treated with azathioprine, and 51% of patients treated with UDCA [29]. On the other hand, in a study of Caucasian patients, 76% of those without cirrhosis at presentation and 78% of those with cirrhosis achieved remission by corticosteroid alone or a combination of corticosteroid and azathioprine [55]. Furthermore, the frequencies of patients who fail corticosteroid treatment are reported to be 7–14%, and onset at an early age, acute presentation, hyperbilirubinemia, and presence of HLA DRB1*03 are associated with treatment failure [55, 59]. Together, these findings indicate that Japanese patients show a favorable response to corticosteroid treatment compared with Caucasian patients.

In a study by Montano-Loza *et al.*, relapse is seen in 86% of AIH patients within 1 year after initial treatment withdrawal [60]. Approximately 50% of these patients relapse within 3 months. Portal plasma cell infiltration in the liver biopsy specimens is predictive of relapse after drug withdrawal [61]. Serum levels of gamma globulin and immunoglobulin G are higher in patients with relapse compared with those with sustained remission [62]. There is no difference in frequencies of relapse after drug withdrawal between patients with and without cirrhosis at presentation. Patients should be treated to achieve normal serum levels of transaminase, gamma globulin, and immunoglobulin G. On the other hand, patients who respond to initial corticosteroid treatment can achieve a sustained remission after treatment withdrawal or after relapse and re-treatment [63].

Corticosteroid. In most patients, prednisolone has been successfully used alone or in combination with azathioprine. In Caucasian patients, prednisolone is initially administered at a dose of 60 mg daily or at a dose of 30 mg daily in combination with azathioprine at 50 mg daily [58]. In Japanese patients, prednisolone monotherapy (30–40 mg/day) or a combination of prednisolone (20–40 mg daily) and azathioprine (50–100 mg daily) is generally performed. In Japanese patients with histological low-grade inflammatory activity, prednisolone at 20 mg daily may be sufficient [3, 4]. Prednisolone is tapered over 6–8 weeks to 5–10 mg daily and should be continued for at least 2 years after the achievement of the normalization of transaminase [58]. Concerning the long-term side effects of corticosteroid, Seela *et al.* [64] have reported that, for a median follow-up of 13.5 years, weight gain, cushingoid feature, and steroid-related osteoporosis were seen in 21%, 7%, and 5% of patients, respectively, although none developed steroid-induced diabetes.

Azathioprine. Azathioprine at 50 mg daily is used in combination with prednisolone as an initial treatment [58]. In patients whose clinical, laboratory, or histological findings worsen despite conventional treatment, azathioprine at 150 mg daily in combination with prednisolone is recommended [58]. Furthermore, Johnson *et al.* [65] reported that, among patients who had achieved remission with a combination treatment of prednisolone and azathioprine and then continued to receive 2 mg/kg azathioprine daily after withdrawal of prednisolone, 83% remained in remission for a median follow-up of 67 months. The use of azathioprine during pregnancy is reported to be relatively safe [66, 67]. The side effects of azathioprine include cholestatic hepatitis, veno-occlusive disease, pancreatitis, severe nausea, and bone marrow suppression. Bone marrow suppression occurs more frequently in cirrhotic patients than non-cirrhotic patients [68, 69].

Ursodeoxycholic acid. UDCA treatment improves serum transaminase levels in patients with AIH type 1, but changes of histological activity before

and after UDCA treatment have been controversial [70, 71]. Furthermore, the duration from the introduction of initial treatment to the normalization of serum ALT levels is longer in UDCA treatment compared with corticosteroid treatment [52]. UDCA treatment should be performed in patients who are not candidates for corticosteroid treatment because of comorbidities such as osteoporosis and diabetes or patients with histological low-grade inflammatory activity and sufficient residual capacity of liver function.

Liver transplantation. Patients who fail immunosuppressive treatment proceed to hepatic failure and require liver transplantation. The 5-year survival rate after liver transplantation has been reported to be 78–100% [72–74]. However, in 41% of patients followed for more than 10 years after liver transplantation, AIH has been reported to recur [75].

Prognosis

In patients with AIH type 1, appropriate treatment improves histological fibrosis, even if cirrhosis is also present [76]. In Caucasians, the prognosis of AIH type 1 has been reported to be similar to that of an age- and sex-matched cohort of disease-free controls from the general population [55]. The 10-year survival has been reported as 89% and 90% in Caucasian patients with and without cirrhosis at presentation, respectively. Similarly, the prognosis of Japanese patients with AIH type 1 is generally good with corticosteroid treatment. The 10-year survival rate and the 10-year HCC-free rate have been reported as 98% and 93%, respectively [3]. On the other hand, the number of patients with AIH type 1 complicated by HCC has increased [77, 78]. Long-standing cirrhosis has been recognized as a risk factor for HCC development. The starting dose of corticosteroid (dose of prednisolone < 20 mg/day), relapse within 3 months after the normalization of serum ALT levels with initial treatment, and elevated serum ALT levels during the follow-up period (> 40 IU/L) have all been significantly correlated with progression of the disease [4]. In particular, elevated serum ALT levels during the follow-up period are associated with HCC development and fatal outcome [3]. Thus, the maintenance of normal serum ALT levels will improve patient prognosis.

Concluding Remarks

AIH is a chronic progressive liver disease caused by an autoimmune mechanism. Although the precise mechanism remains to be fully clarified, multiple factors such as molecular mimicry, a genetic background including HLA class II, and defective regulatory T cell function are involved in the pathogenesis of AIH. Typical clinical features include histological interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies, but patients with atypical forms have been recognized and thus the clinical features have been diversified. Immunosuppressive treatments including corticosteroid and/or azathioprine are effective, and the long-term prognosis is good. UDCA is also effective but needs further evaluation for the long-term prognosis. Liver transplantation is the indicated treatment for patients with hepatic failure, though AIH recurs in 41% of patients after liver transplantation.

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