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Guideline

KASL clinical practice guidelines for management of autoimmune hepatitis 2022

The Korean Association for the Study of the Liver (KASL)*

Keywords: Autoimmune hepatitis; Diagnosis; Treatment; Guidelines

PREAMBLE

Purpose and scope

Autoimmune hepatitis (AIH) is an inflammatory liver disease of unknown etiology caused by an autoimmune mechanism. It can occur in all age groups and manifest as almost every type of liver disease, including asymptomatic liver enzyme elevation, acute hepatitis, acute liver failure (ALF), chronic hepatitis, or cirrhosis. There are no specific tests for diagnosing AIH, and diagnosis can be made by synthesizing several findings that are relatively characteristic of AIH. Immunosuppressive therapy based on glucocorticoids is the first-line treatment and is very effective for most patients. However, if the diagnosis is delayed or primary treatment is ineffective, serious complications, such as decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation, could occur.

As AIH is a rare disease and responds well to first-line treatment, high-quality research on second-line treatments or specific situations is limited. Recommendations based on high-quality evidence are also limited, even in the U.S. or European guidelines. In South Korea, the prevalence of AIH is lower than that in the West, and research and awareness on AIH are lacking compared to viral hepatitis, which has a high disease burden. Moreover, South Korea still has no official treatment guidelines for AIH.

Therefore, we have systematically reviewed Korean and international studies to prepare appropriate guidelines based on evidence and to reflect domestic conditions as much as possible. In case related studies on clinically essential issues are lacking, we tried to present consensus opinions of experts. These guidelines have been developed through the reviews of medical evidence by experts to provide a practical reference for the treatment, research, and education of AIH. They are not absolute standards for treatment, and the best

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choice of practice for individual patients may vary depending on the individual circumstances. If relevant evidence based on new research results is accumulated in the future, these guidelines can be revised and supplemented. The guidelines cannot be modified, transformed, or reproduced without permission.

Target population

The target population of these guidelines include adults, adolescents, and pediatric patients with AIH.

Intended users

The following guidelines aim to provide clinical information useful for decision-making of healthcare providers involved in the diagnosis and treatment of AIH patients and to raise awareness of AIH among them, ultimately reducing morbidity and mortality and increasing the quality of life for AIH patients. In addition, these guidelines are intended to provide specific and practical information to resident physicians, practitioners, and trainers.

Guideline development group, process, and funding source

The Clinical Practice Guideline Committee for the Management of AIH (committee) was organized in accordance with proposals approved by the KASL Board of Executives. The committee consists of 12 hepatologists, one clinical pathologist, one pathologist, one pediatrician specializing in hepatology, and one methodology expert (Supplementary Table 1). All expenses were paid by KASL, and the financial support did not affect the independence of the contents of the guidelines. Each member of the committee collected, analyzed relevant evidence, and wrote the manuscript in his or her field. The timeline of the guideline development process is shown in Supplementary Table 2. Conflicts of interest among the members are summarized in Supplementary Table 3.

Literature search for evidence collection

The committee collected and analyzed relevant Korean and international literature through PubMed, MEDLINE, KoreaMed, KMBASE, RISS, and KISS to establish the guidelines based on the latest research and evidence. Only Korean and English literature were searched, and the search terms included "AIH" or "autoimmune liver disease" and specific terms of the subject.

Levels of evidence and grades of recommendations

The literature collected for evidence was analyzed through systematic review, and the levels of evidence were classified based on the revised Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) with modification (Table 1).[1-3] They were categorized based on the possibility of changes in the assessment through further research as follows: high (A), with the lowest possibility; moderate (B), with certain possibility; and low (C), with the highest possibility. Specifically, depending on the type of study, randomized controlled trials start at a high level of evidence (A) and observational studies start at a low level of evidence (C). Considering factors affecting the study's quality, the evidence level was raised or lowered further.[2] The strength of recommendation was suggested to be either strong (1) or weak (2), according to the GRADE system.[4] It was determined based on the clinical effects of recommendation, patient's receptivity, and socioeconomic aspects, as well as the level of evidence. For

Abbreviations:

6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; 6-TGN, 6-thioguanine nucleotides; ACLF, acute on chronic liver failure; AIH, autoimmune hepatitis; AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibody to liver kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, area under the receiver operating characteristic curve; AZA, azathioprine; CI, confidence interval; CT, computed tomography; DILI, drug-indued liver injury; ELISA, enzyme-linked immunosorbent assay; FIB-4, fibrosis-4 index; FRAX, Fracture Risk Assessment Tool; GGT, gamma-glutamyl transferase; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HAI, hepatitis activity index; HLA, human leukocyte antigen; HR, hazard ratio; IFA, indirect immunofluorescence assay; IgG, immunoglobulin G; INR, international normalized ratio; LC, liver cirrhosis; MMF mycophenolate mofetil; mTOR, mammalian Target of Rapamycin; NUDT15, Nudix hydrolase15; OR, odds ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; p-ANNA, perinuclear antineutrophil nuclear antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PT, prothrombin time; RR, relative risk; SMA, smooth muscle antibody; SWE, shear wave elastography; TNF, tumor necrosis factor; TPMT, thiopurine S-methyltransferase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal range

example, a strong recommendation indicates that interventions could be applied in most patients with solid certainty in terms of a greater possibility of desirable effects, high-quality evidence, presumed patient-important outcomes, cost-effectiveness, preference, and compliance. A weak recommendation indicates a suggestion made with less certainty, which could be considered favorable for many patients. Alternative interventions could be chosen for "weak recommendations" according to the preferences of patients or medical practitioners.

List of key questions

The Clinical Practice Guideline Committee for the Management of AIH selected the following key questions and presented evidence and recommendations for them.

1. What are the incidence and prevalence of AIH?
2. What are the clinical features of AIH?
3. What are the characteristics of AIH type 1 and type 2?
4. What are the characteristics of overlap syndromes?
5. What are the concurrent autoimmune diseases of AIH?
6. How does AIH differ from AIH-like drug-induced liver injury (DILI)?
7. How is AIH diagnosed?
8. What autoantibody tests are required to diagnose AIH?
9. What are the characteristic histologic findings for AIH?
10. What are the diagnostic criteria for AIH, and what is the diagnostic usefulness of each criterion?
11. What are the proven non-invasive methods to assess liver fibrosis in AIH?
12. What should be evaluated before starting treatment for AIH?
13. Are pre-tests required before azathioprine (AZA) treatment for AIH?
14. What are the criteria for initiating immunosuppressive therapy for AIH?
15. What is the first-line treatment for AIH?
16. How is the treatment response for AIH evaluated?
17. What should be monitored during the immunosuppressive treatment for AIH?
18. What are the side effects of AIH treatment?
19. What are the criteria for terminating immunosuppressive treatment for AIH?
20. How are patients with AIH followed after the termination of immunosuppressive treatment?
21. How is recurrent AIH treated?
22. What is the second-line treatment for AIH?
23. What is the treatment for pediatric and adolescent patients with AIH?
24. What is the treatment for pregnant patients with AIH?
25. What is the treatment for elderly patients with AIH?
26. What is the treatment for overlap syndromes?
27. What is the treatment for AIH with non-alcoholic fatty liver disease?
28. What is the treatment for AIH accompanied by viral hepatitis?
29. What is the treatment for AIH which recurs or develops after liver transplantation?

Table 1. GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) system

Quality of evidence		Criteria	
High quality	A	Further research is very unlikely to change our confidence in the estimate of effect.	Randomized trials without important limitations
Moderate quality	B	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Randomized trials with important limitations or observational studies with special strengths
Low quality	C	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Observational studies without special strengths or important limitations
Strength of recommendation		Criteria	
Strong	1	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.	
Weak	2	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption.	

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30. What is the prognosis of AIH?
31. What are the complications of AIH?
32. What is the incidence of hepatocellular carcinoma in patients with AIH, and who is at high risk, and who needs surveillance?

In addition, the committee attempted to present evidence and recommendations by conducting a systematic review on the following topics: 1) Is there a difference between low-dose prednisolone with or without AZA and high-dose prednisolone with or without AZA in terms of efficacy and side effects as a first-line treatment for patients with AIH except acute severe AIH or hepatic failure?

Internal & external review, and approval process

Manuscripts and recommendations prepared by each member were reviewed for content integrity and validity of evidence through several meetings at the committee, and the quality of the guidelines was evaluated according to the criteria of AGREE II (Appraisal of Guidelines for Research and Evaluation II). The recommendations were assessed and revised based on the critical review by the Delphi Committee, consisting of 11 experts in the field of hepatology belonging to the KASL (Supplementary Table 4). The guidelines were reviewed at a meeting of an external review board, consisting of seven specialists in the field of hepatology, and at a symposium open to all KASL members and the public, and they were then further modified. The final manuscript was endorsed by the Board of Executives of KASL.

Release of the guideline and plan for updates

The KASL Clinical Practice Guideline for the management of AIH was released at the 6th Korea Digestive Disease Week 2022 (December 1, 2022) and will be published in *Clinical and Molecular Hepatology*. The Korean version of the guideline is available on the KASL website (http://www.kasl.org). The KASL plans to update the guidelines when new significant evidence is accumulated, and revision of the guidelines is deemed necessary to improve the national health of Korea.

EPIDEMIOLOGY

Incidence

According to a meta-analysis, the global annual incidence of AIH was 1.37 per 100,000 persons (95% confidence interval [CI], 0.95–18.0) in 2019. The regional annual incidence in Asia, Europe, and America were 1.31, 1.37, and 1.00 per 100,000 persons, respectively.[5] An analysis based on data from the rare and intractable disease registry program in the Korean National Health Insurance system presented that the age- and sex-adjusted AIH incidence rate in South Korea during 2011–2013 was 1.07 per 100,000 persons, which was similar to the global incidence. From 2009 to 2013, a total of 4,085 cases of AIH had been diagnosed, and the gender-adjusted annual AIH incidence rate was 0.31 per 100,000 in males and 1.83 per 100,000 in females. The incidence of AIH in females was 6 times that in males, and the mean age was 55 years (55 years in females, and 53 years in males). Age-specific incidence rate increased with age, and the peak age was 60s, with an annual incidence of 3.1 per 100,000 persons (Fig. 1A).[6] While two peaks in incidence were shown in people in their late 10s and 50s to 70s in studies from Denmark, Sweden, and New Zealand,[7-9] one peak was shown in the 60s age group in studies from United Kingdom and South Korea.[6,10] In a Danish study, the annual incidence of AIH increased from 1.37 per 100,000 persons in 1994 to 2.33 per 100,000 persons in 2012,[7] while the incidence did not increase in Sweden.[8] To date, there is no available data regarding the trend of AIH incidence in South Korea.

Prevalence

The global prevalence of AIH was 17.44 per 100,000 persons (95% CI, 12.01–22.87). The regional prevalence of AIH for Asia, Europe, and America was 12.99, 19.44, and 22.80 per 100,000 persons, respectively.[5] Meanwhile, according to a South Korean study including data from 2009 to 2013, the AIH prevalence was 4.82 per 100,000 persons and the gender-specific prevalence was higher in females, which was 8.35 per 100,000 persons in females, and 1.30 per 100,000 persons in males. The number of female patients was high among those in their 50s and 60s, and the peak prevalence for females was shown in their 60s (8.35 per 100,000 persons), and that for males was observed in their 70s (1.30 per

100,000 persons) (Fig. 1B).[6] The prevalence was the highest among people in their 50s in New Zealand,[9] and those in their 70s in Sweden and the United States.[8,11] Since 2000, the trend of prevalence increased in Sweden, New Zealand, and Japan.[8,9,12] The prevalence in South Korea increased from 3.9 per 100, 000 persons in 2009 to 5.76 per 100,000 persons in 2013, but further subsequent data are needed to evaluate the trend of AIH prevalence.

Genetic predisposition

It is well-known that human leukocyte antigen (HLA) *DRB1*03* or *DRB1*04* predisposes the onset of AIH and influences the natural course of the disease and treatment response.[13-15] In a study in South Korea, the frequencies of *DRB1*0405* or *DQB1*0401* were significantly increased in patients with AIH type 1 compared to the controls (odds ratio [OR], 3.74 & 3.95), and AIH type 1 was associated with the QRRAA motif at position 70-74 of the *HLA-DRB1* molecule.[16]

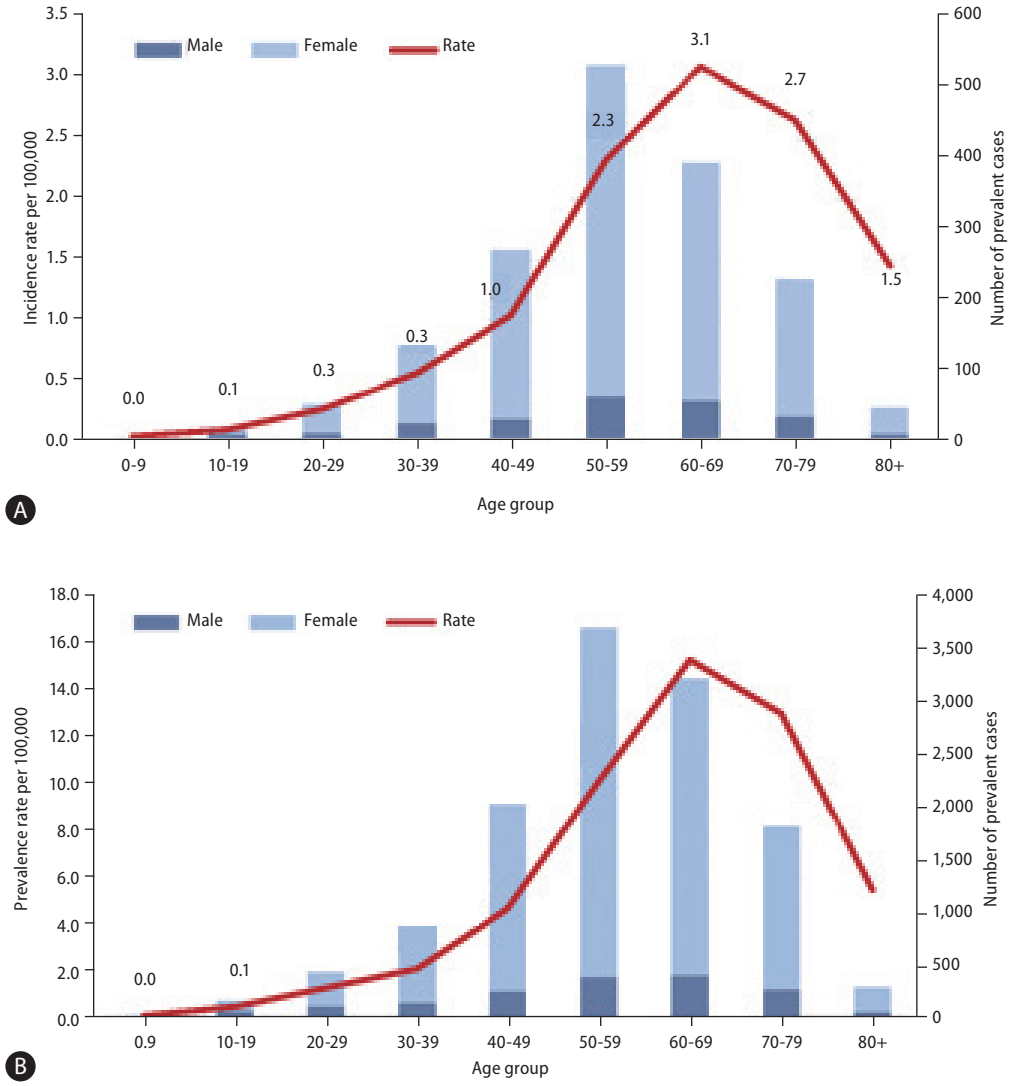

Figure 1. Epidemiology of autoimmune hepatitis in South Korea. (A) Average annual gender-adjusted incidence rate per hundred thousand population and incident cases (2011–2013) of autoimmune hepatitis by age (B) Average gender-adjusted prevalence rate per hundred thousand population and prevalent cases (2009–2013) of autoimmune hepatitis by age.

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Summary

The annual incidence of AIH in South Korea was reported as 1.07 per 100,000 persons, and the prevalence was 4.82 per 100,000 persons. AIH occurred 6 times more frequently in females than in males. The incidence of AIH presented one peak among people in their 60s in South Korea, which was in contrast to a bimodal peak shown in those in their late teens and 60s in Western countries.

CLINICAL MANIFESTATIONS

AIH usually develops insidiously; however, the spectrum of symptoms and clinical manifestations are broad, ranging from asymptomatic to acute hepatitis, and AIH may also develop as fulminant hepatitis (Fig. 2).[17] In addition, liver fibrosis has already progressed at the time of AIH diagnosis, and cirrhosis may be already present, or it may even appear as an acute exacerbation of cirrhosis.[18] In a Korean population study, 31–37% of patients were asymptomatic at the time of AIH diagnosis, and 13–32% of patients had cirrhosis as well.[19] Therefore, AIH should be considered as a differential disease in most liver diseases regardless of the degree of activity or fibrosis.

Typical AIH presents as a form of chronic hepatitis with autoantibodies, hypergammaglobulinemia, and interface hepatitis in liver biopsy. Nonspecific fatigue is the most common. Loss of appetite, weight loss, muscle aches, joint pain, jaundice, and amenorrhea may be present, but low-grade fever and rash are less common.[20]

Asymptomatic AIH

Patients who met the diagnostic criteria for AIH but showed no symptoms with elevated liver enzyme accounted for 25–37% of patients with AIH.[19,21] In patients with asymptomatic AIH, liver enzyme elevation may improve spontaneously; and in a previous study, symptoms appeared in 25.8% of the patients, and the average period until symptom onset was 2.00±2.46 years.[22,23] Compared to symptomatic AIH patients, asymptomatic AIH patients showed no difference in terms of age, sex ratio, disease progression, and histological findings, but they had significantly lower level of liver enzyme elevation and immunoglobulin G (IgG).[24] In a Canadian study, asymptomatic AIH patients had no significant difference in 10-year survival compared to AIH patients with symptoms (80% vs. 83.8%, P=0.8).[22]

Acute severe AIH and acute liver failure

Acute severe AIH is defined as jaundice with a prothrombin

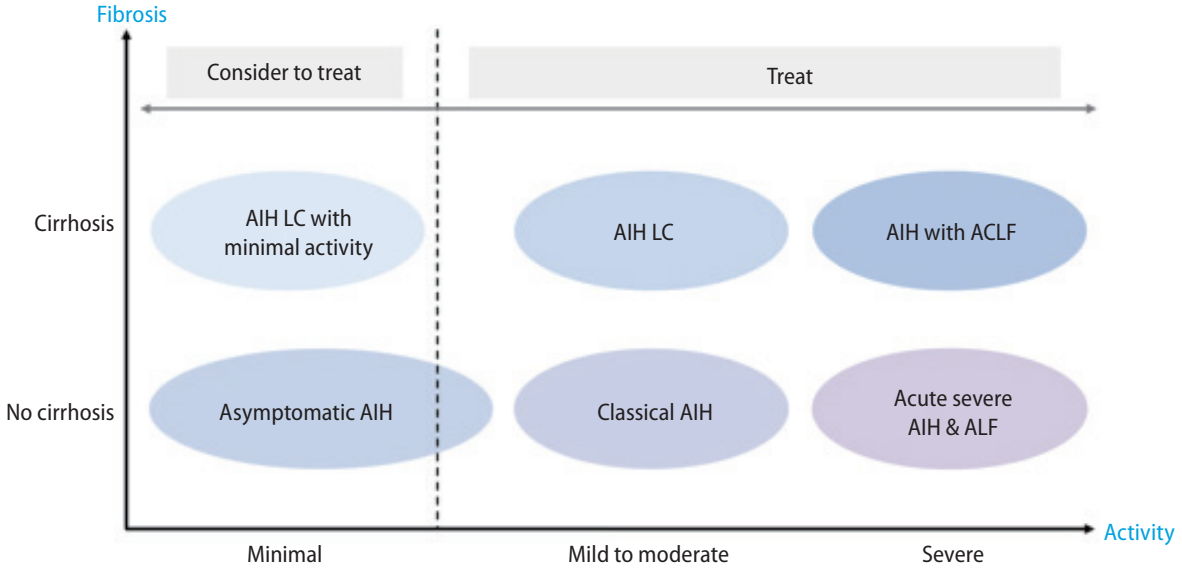

Figure 2. Clinical spectrum of autoimmune hepatitis. ACLF, acute on chronic liver failure; AIH, autoimmune hepatitis; ALF, acute liver failure; LC, liver cirrhosis.

time (PT) international normalized ratio (INR) of 1.5 to 2 but without hepatic encephalopathy due to AIH.[21] ALF with AIH was defined as a PT INR of 2 or greater or the development of hepatic encephalopathy within 26 weeks of AIH onset.[21] At the time of AIH diagnosis, about 25% of AIH patients showed acute presentation and 3–6% showed AIH with ALF.[21,25] Among patients with acute severe AIH, 29–39% of patients showed negative or weakly positive anti-nuclear antibodies (ANA) and 25-39% showed normal serum IgG.[26,27] In a recent study, heterogeneous hypo-attenuated region of the liver on non-contrast computed tomography (CT) scan was observed in 65% of AIH patients with ALF, whereas it was shown in only 2.2% of viral hepatitis patients with ALF.[28] These CT findings may be helpful for the diagnosis of AIH with ALF.

AIH with cirrhosis

Approximately 25–33% of AIH patients had liver cirrhosis (LC) at the time of AIH diagnosis regardless of clinical symptoms. Furthermore, it may present as decompensated cirrhosis or acute-on-chronic liver failure (ACLF).[18] In a retrospective cohort study in the United States, the male gender, black or Hispanic race, older age (≥60 years), and lower education level were independent risk factors associated with cirrhosis at AIH diagnosis.[29] AIH patients with cirrhosis sometimes show burnt-out cirrhosis, in which histological characteristics of AIH are not observed. In such cases, the diagnosis of AIH can be made considering accompanying extrahepatic autoimmune diseases, the presence of autoantibodies, and past medical history.[20,30] In AIH patients with ACLF presentation, the proportion of ANA-negative was as high as 49%. Liver histology showed a moderate or high grade of interface activity in 90% and hepatic necrosis in 56% of the patients.[31]

Type 1 and type 2 AIH

AIH can be classified into two types depending on the specific autoantibodies. Type 1 is characterized by the presence of ANA, smooth muscle antibody (SMA), and/or anti-actin antibody. Type 2 is characterized by the presence of antibody to liver kidney microsome type 1 (anti-LKM1) and/or antibody to liver cytosol type 1(anti-LC1), usually with the absence of ANA and SMA.[21,32,33] About 20% of patients with AIH may be negative for ANA, SMA, and anti-LKM1, even though they show clinical features of AIH. In such cases, antibody to soluble liver antigen (anti-SLA), an antibody test such as perinuclear antineutrophil cytoplasmic antibody (p-ANCA), can be additionally performed.[21]

Type 1 AIH can occur at any age, but the onset peaks mainly around puberty and around the age of 60. Type 2 primarily occurs in children under 14 years of age or young adults, and is known to be very rare. A Korean study reported that anti-LKM1 was positive in about 1–3% of adult patients with AIH.[19,34] In a Korean single-center study of 14 pediatric patients with AIH, none of the patients were positive for anti-LKM1.[35] Type 2 AIH is also known to be very rare in East Asian countries, such as Japan and Taiwan.[34,36] However, type 2 AIH is relatively common in South Asian countries, the United States, and Europe, and 13.2–16% of all pediatric patients with AIH have been reported as type 2 AIH in Malaysia and Canada.[36-38] In both types 1 and 2 AIH, IgG is often elevated but may be normal in the early stages of the disease, and sometimes normal or even lower in type 2.[37,39] Type 1 AIH presents mainly in adults as acute or chronic non-specific symptoms such as fatigue, nausea, abdominal pain, and joint pain.[40] In type 2 AIH, acute onset occurs in 31–40% of the cases, and up to about 25% is known to develop in the form of ALF; and relatively many cases are unresponsive to treatment.[21,32,41-43]

Autoantibody-negative AIH (seronegative AIH)

Autoantibody-negative AIH is defined as patients clinically and pathologically compatible with AIH, but without ANA, SMA, or anti-LKM; and accounts for 19–34% of AIH patients.[21] Even if autoantibodies are negative at the time of diagnosis, autoantibodies can become positive later in the course of the disease. In a retrospective cohort study, 60% of patients with autoantibody-negative AIH showed seroconversion up to 5 years of follow-up.[44] IgG4-related AIH, which showed high serum IgG4 levels and prominent IgG4-positive plasma cell infiltration in the liver, was 3.3–25%.[45] Autoantibody-negative AIH is diagnosed by clinical suspicion based on a diagnostic scoring system and the response to glucocorticoid treatment.[46] Autoantibody-negative AIH showed lower serum IgG level compared to autoantibody-positive AIH,[47] and was relatively high at 29–39% in the AIH subgroup which presents as acute hepatitis or ACLF. Therefore, these patients are likely to be diagnosed with hepatitis of unknown etiology, and clinical suspicion and empirical treatment are essential for the di-

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agnosis.[27,31] The 3-month biochemical response rate of autoantibody-negative AIH was 67–83%, which was similar to that of autoantibody-positive AIH.[48]

Overlap syndromes

Overlap syndromes are defined as cases in which AIH is accompanied by other autoimmune diseases such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), or IgG4-related cholangitis clinically, biochemically, serologically, and histologically.[49]

AIH-PBC overlap syndrome

The prevalence of autoimmune hepatitis-primary biliary cholangitis (AIH-PBC) overlap syndrome was reported as 8–10% among AIH patients, and 7.4–11.7% in Korean studies.[6,50,51] In 8–12% of patients with AIH, antimitochondrial antibody (AMA) may be positive despite no histologic findings of bile duct damage or loss, and these patients respond well to glucocorticoid therapy alone.[52] Therefore, AMA positivity alone should not be diagnostic for AIH-PBC overlap syndrome. AIH-PBC overlap syndrome can be diagnosed simultaneously or sequentially. In a retrospective cohort study, 13.8% of the patients were diagnosed with AIH-PBC overlap syndrome, 7.8% were diagnosed with AIH and PBC simultaneously, 1.8% were diagnosed with AIH first, and 4.3% were diagnosed with PBC first.[53]

AIH-PSC overlap syndrome

Adult patients with autoimmune hepatitis -primary sclerosing cholangitis (AIH-PSC) overlap syndrome are usually diagnosed first with AIH and then with PSC several years later.[51] AIH-PSC overlap syndrome can be suspected in AIH patients who have shown cholestatic liver biochemistry and insufficient response to immunosuppressive treatment. AIH-PSC overlap syndrome has been reported in 6-11% of AIH patients in the West; however, it is very rare in the East.[54] Patients with AIH-PSC overlap syndrome were younger (24 years old vs. 39.2 years old), and had higher levels of alkaline phosphatase [ALP]; 200.7 vs. 111.3 U/L) and bilirubin (2.7 vs. 1 mg/dL) at the time of diagnosis compared to patients with AIH alone.[55]

Concurrent autoimmune diseases

About 14–44% of AIH cases are associated with other autoimmune diseases.[56-58] Autoimmune thyroid disease (AITD) is the most common concurrent autoimmune condition associated with AIH. Type 1 AIH is often associated with AITD, while type 2 AIH is generally associated with type 1 diabetes, AITD, and autoimmune skin diseases, such as vitiligo, leukocytoclastic vasculitis, urticaria, alopecia areata, etc.[23,26,56-58] Other concurrent autoimmune conditions include rheumatoid arthritis (RA), mixed connective tissue disease, autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura, polymyositis, uveitis, Sjögren syndrome, systemic lupus erythematosus (SLE), and ulcerative colitis.[59]

According to a recent report by South Korean investigators using the population-based National Health Insurance Service (NHIS) and the Rare Intractable Disease registration program between 2009 and 2013, the most common concurrent autoimmune disease was thyroid disorders, accounting for 10.5% of all cases among 3,783 patients with AIH. The second most common condition was SLE, accounting for 2.2%, followed by RA at 0.4% and systemic sclerosis at 0.2%.[6]

In a small study on 205 North American adults diagnosed with AIH, concurrent extrahepatic autoimmune diseases occurred predominantly in women (85%).[60] Co-occurring diseases varied by age. AITD, inflammatory bowel disease (IBD), and AIHA predominantly affected younger adults under the age of 30, while autoimmune thyroiditis and RA were more frequently observed among adults aged over 60.[60] Furthermore, a small study on 86 North American adults diagnosed with AIH revealed that *HLA DRB1*04:01*-positive patients were more likely to have concurrent extrahepatic autoimmune diseases.[13] A questionnaire survey on 306 patients with AIH reported a higher prevalence of autoimmune disease in the first-degree relatives of patients than in the healthy controls (1,162 individuals; 55.9% vs. 35.7%).[61]

Autoimmune thyroid diseases

AITD is the most common concurrent autoimmune condition associated with AIH (10–23%). Hashimoto's thyroiditis is associated with AIH, accounting for approximately 10.2–14.1% of all concomitant autoimmune diseases, followed by Grave's disease at about 3–6%.[58] A retrospective study reported elevated IgG in patients with AIH accompanied by AITD.[62]

Systemic lupus erythematosus

Approximately 2.8-3% of patients with AIH are accompanied by SLE.[58,63] A case report documented an occurrence of complications, such as myocarditis and thrombotic thrombocytopenic purpura, in an AIH patient with SLE.[63] On the contrary, 2.7–4.7% of patients with SLE were accompanied by AIH, and 19.4% of SLE patients with high liver enzyme levels were associated with AIH.[64,65] Moreover, 1.7% of SLE patients who received a biopsy due to suspected liver disease were found to have chronic hepatitis or LC.[63,66] A retrospective study reported that patients with AIH accompanied by SLE had higher IgG levels, and those with higher IgG had a poor prognosis.[67]

Sjögren syndrome and rheumatoid arthritis

Sjögren syndrome is observed in about 2.8–7% of patients with AIH.[58,68] The association between Sjögren syndrome and liver disease was first reported in 1954.[69] The prevalence of AIH among patients with Sjögren syndrome is not yet clearly known, with prevalence estimates ranging widely from 4 to 47%.[70] RA develops in approximately 2–4% of patients with AIH.[58,68,71] Immunosuppressive therapy is a favorable treatment option for RA and prevents joint deformity.[71] RA more commonly occurs in older AIH patients than in younger AIH patients.[68,71]

Inflammatory bowel disease

IBD occurs in about 2–11.4% of AIH patients.[72-75] AIH is observed in approximately 3.7–11.4% of IBD patients.[58,73] In particular, ulcerative colitis is primarily associated with PSC, but AIH can also occur in 2–8% of AIH patients.[71] When proctoscopic examination was performed annually in 105 AIH patients receiving glucocorticoid treatment, ulcerative colitis was detected in 12 patients (11.4%).[73] Meanwhile, patients with AIH were less likely to develop Crohn's disease at a frequency of 1–6%.[71]

In addition to the conditions mentioned above, multiple sclerosis occurs in about 0.17% of AIH patients, and this proportion is higher than the 0.02% prevalence of the general population.[76,77] Furthermore, AIH can also be rarely associated with leukoplakia, alopecia areata, celiac disease, type 1 diabetes mellitus, idiopathic thrombocytopenic purpura, pulmonary fibrosis, Raynaud's phenomenon, etc.

Summary

AIH is usually manifested in the form of chronic hepatitis, but it can also manifest in the form of various liver diseases, such as asymptomatic, acute hepatitis, acute severe hepatitis including fulminant hepatitis, cirrhosis, and acute exacerbation of cirrhosis.

AIH can be divided into type 1 (ANA, SMA) and type 2 (anti-LKM1, anti-LC1) based on specific autoimmune antibodies, and type 2 AIH is very rare in South Korea.

A variety of autoimmune diseases accompany AIH patients, and AITD is the most common type.

DIAGNOSIS

Diagnostic criteria

The diagnosis of AIH is based on the characteristic clinical and laboratory findings (elevated serum aspartate aminotransferase [AST], alanine aminotransferase [ALT] and increased IgG concentration), the presence of characteristic autoantibodies, and compatible histological abnormalities (Figs. 3, 4). AIH lacks a signature diagnostic marker, and the diagnosis requires the exclusion of other diseases (viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, DILI, Wilson's disease, hereditary hemochromatosis, etc.).[18,21,78]

Although serum bilirubin and aminotransferase are markedly raised, normal or mildly elevated cholestatic enzymes are characteristic of AIH. The elevation of serum IgG level is a common feature, but IgA and IgM levels are usually normal.[78-81] In a European multicenter study, IgG was normal in about 10% of the patients; and even in these patients, clinical features were similar to typical AIH.[82] IgG was normal in 25–39% of AIH with acute presentation, according to studies from Japan.[26,27,83]

Liver biopsy, which is an essential procedure in the diagnosis of AIH, was done in 54–75% of the Korean AIH patients.[19] Liver histology is important not only in confirming the clinical diagnosis of AIH, but also in differential diagnosis of AIH. Liver biopsy is considered a prerequisite for the diagnosis of AIH. The general view is that AIH cannot be diagnosed without compatible histological findings, considering the differ-

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entiation from other diseases and the discrimination of overlapping syndromes, although there is an opinion that a biopsy may not be necessary if the laboratory features are sufficiently typical.[18,21,26,78,84] Therefore, liver biopsy is essential

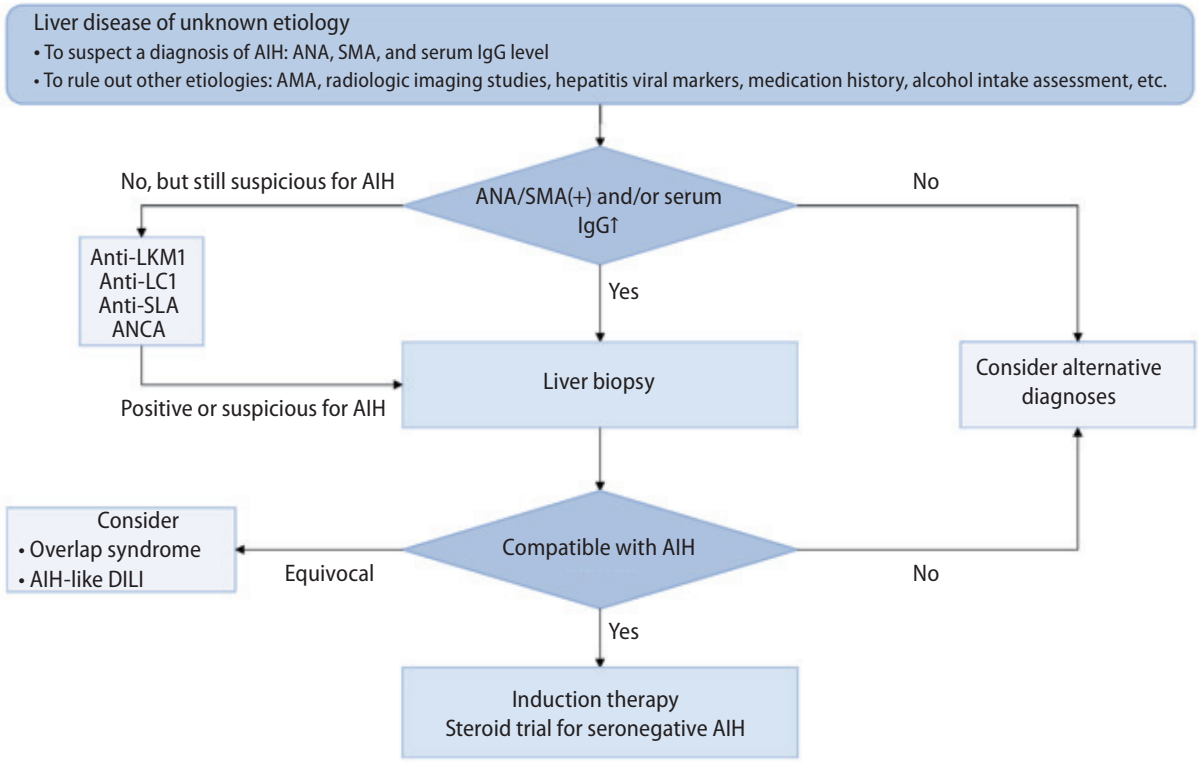

Figure 3. Diagnostic algorithm of autoimmune hepatitis. AIH, autoimmune hepatitis; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibody to liver kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; DILI, drug-induced liver injury; IgG, immunoglobulin G; SMA, smooth muscle antibody.

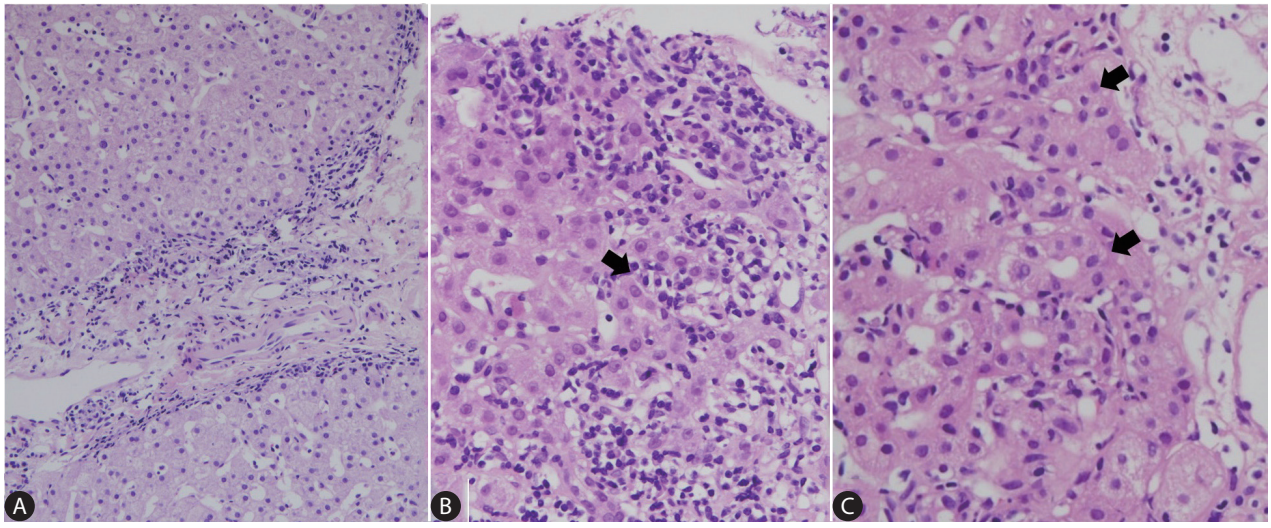

Figure 4. Histopathology of autoimmune hepatitis. (A) The microscopic features of autoimmune hepatitis. Mononuclear cells, including lymphocytes and plasma cells, are seen at the interface between the portal tract and hepatic lobule (H&E stain, x100). (B) Clusters of plasma cells (arrow) are often seen at high-power magnification (H&E stain, x400). (C) Hepatocyte rosettes (arrows) are shown (H&E stain, x400).

if there are no contraindications.

Autoantibodies

Autoantibody ANA and SMA are used as screening tests for AIH.[85] Anti-LKM1, anti-LC1, anti-SLA, and ANCA can also be tested if ANA and SMA are negative. HEp-2 cells for ANA and rodent tissues for SMA are used as the target antigens in indirect immunofluorescence assays (IFA), which are the primary methods for detecting ANA and SMA (Table 2). Multiple autoimmune liver disease antibodies can be evaluated simultaneously by immunoblot for anti-LKM1, anti-LC1, and anti-SLA. The conventional serum dilution that tested positive for ANA and SMA using the IFA method is 1:40 for adults and 1:20 for children, and it is 1:10 for anti-LKM1 and anti-LC1. Repeat testing may be necessary for an appropriate diagnosis and classification if the initial autoantibody test is negative.

Since ANA targets antigens whose specificity has not been determined, testing using enzyme-linked immunosorbent assay (ELISA) can result in false negatives in about one-third of the patients.[86] Actin is one of the cytoskeletal antigens that SMA reacts to, and anti-actin is found in about 40% of cases.[20] When both ANA and SMA are detected, the diagnostic value would be high.[20] Anti-SLA has diagnostic relevance as it is the sole disease-specific autoantibody for AIH.[87] However, a solid phase immunoassay test, such as ELISA or immunoblot, should be carried out since it cannot be detected by the IFA method. The serological markers of type 2 AIH, anti-LKM1 and anti-LC1 should be ruled out as they can be found in 5–10% of adult and pediatric patients with chronic HCV infection. The ANCA test of the IFA method can be used when the results of the ANA, SMA, and anti-SLA tests are negative. In some patients with type 1 AIH, perinuclear anti-neutrophil nuclear antibody (p-ANNA) or p-ANCA may be the only serological markers.[88,89] AMA, a serological marker specific to PBC, is performed for the differential diagnosis of overlap syndrome and can be detected in 8–12% of patients with typical AIH.[52,90] Autoantibody titers in pediatric patients can be useful biomarkers reflecting disease activity and may also be useful for monitoring treatment response. Serology laboratories and physicians need to increase their expertise and communicate closely in interpreting the autoimmune liver disease serology to provide maximum benefits to patients. If the diagnosis is uncertain, it is necessary to refer a serological test to a specialized reference laboratory for a complete evaluation.

Histological findings

Histopathologically, the typical AIH case demonstrates a hepatitic picture with portal lymphoplasmacytic infiltration and interface hepatitis (Fig. 4).[81,91-93] Plasma cells are often

Table 2. Characteristics of autoantibodies in AIH

Autoantibody	Method of detection	Frequency	Characteristics
ANA	IFA ELISA/Immunoblot	75–95%	AIH-1 Homogenous pattern in 2/3; speckled or nucleolar in 1/3 on HEp-2 cell using IFA
SMA	IFA ELISA/Immunoblot (Actin)	–75%	Strongly favors AIH-1, particularly when combined with ANA at high titers
Anti-LKM1	IFA ELISA/Immunoblot	70% in AIH-2	AIH-2 after excluding hepatitis C Titer correlates with disease activity.
Anti-LC1	IFA ELISA/Immunoblot	30% in AIH-2	AIH-2 after excluding hepatitis C
Anti-SLA	ELISA/Immunoblot	20–30% in AIH-1 and AIH-2	Specific for AIH Associated with more severe disease
p-ANNA	IFA	20–96% in AIH-1	Detected as the only serological marker in suspected AIH-1 with negative ANA, SMA, and anti-SLA

AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; ANA, antinuclear antibody; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibody to liver kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; ELISA, enzyme-linked immunosorbent assay; IFA, indirect immunofluorescence assay; p-ANNA, perinuclear antineutrophil nuclear antibody; SMA, smooth muscle antibody.

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abundant. Various degrees of lobular necroinflammation have been observed. Fibrosis typically begins from the portal tracts and eventually progresses to cirrhosis. Periportal hepatocytes often appear in rosette configuration (hepatocytic rosettes), and emperipolesis may also be seen. AIH may demonstrate an acute hepatitis pattern on histology, characterized by prominent lobular necroinflammation and zone 3 confluent necrosis, with relatively mild or minimal portal changes.[93-95] In addition, fibrosis may be absent in the earlier stages of AIH. Once AIH progresses to cirrhosis, the typical histological features, such as portal inflammation and interface activity, may become inconspicuous (so-called "burnt out" AIH); and at this stage, it is often difficult to distinguish AIH-cirrhosis from cirrhosis of other etiologies. Bile duct injury is not a typical feature of AIH, and if marked bile duct injury is seen in a background of otherwise typical AIH, the possibility of overlap syndrome (AIH-PBC, AIH-PSC) may be entertained. Drug/toxin-induced liver injury may present with AIH-like histology; and therefore, it is always important to clinically exclude this possibility.

According to the 1999 revised scoring system and the 2008 simplified system, the presence of portal lymphoplasmacytic infiltration, interface hepatitis, hepatocytic rosettes, and emperipolesis are the key histological features for a diagnosis of AIH.[81,91] However, these staging systems have some limitations: hepatocytic rosettes and emperipolesis are not specific for AIH, as they may be seen in the setting of severe hepatocyte injury and regeneration of any etiology; and AIH with acute hepatitis patterns are less likely to qualify as definite AIH with these scoring systems due to the lack of portal changes on histology.[92,93,96] Recent consensus documents suggest that the possibility of AIH could be suggested for cases with less than mild portal changes, if there is at least moderate lobular necroinflammation and other etiologies have been sufficiently excluded.[92,93]

For the diagnosis and staging of AIH, it is important that a sufficient number of portal tracts are included in the liver biopsy sample. It is recommended that the biopsied tissue is at least 1.5 cm in length and that wider cores are obtained to ensure evaluation of the entire circumference of the portal tract.[97-99] In order to accurately evaluate the degree of fibrosis, collagen stains, such as Masson's trichrome, are necessary in addition to the routine hematoxylin-eosin stains.

Diagnostic scoring sytems

A diagnostic scoring system was proposed by the International Autoimmune Hepatitis Group (IAIHG) to help diagnose atypical cases as well as typical cases of AIH, quantify diagnoses, and enable objective comparison. In 1999, a revised original scoring system was announced, and in 2008, a simplified scoring system was also developed (Tables 3, 4).[81,91,100] In South Korea, diagnoses were also based on the revised original scoring system and simplified scoring system.[19] The revised diagnostic scoring system is known to help diagnose patients with complex or atypical features, whereas the simplified scoring system is more accurate in typical patients.[101] In a Japanese study, the revised scoring system showed 100% sensitivity and 93% specificity, and the simplified scoring system showed 85% sensitivity and 99% specificity.[102] In a Korean study, the diagnostic sensitivity and positive predictive value of the simplified criteria compared with the revised original criteria were 69.9% and 86.4%, respectively.[34,103] Therefore, considering the high sensitivity of the revised scoring system and the high specificity of the simplified scoring system, if the score calculated by the simplified scoring system is low, reassessment with the revised scoring system should be considered.[101]

The revised diagnostic scoring system can be applied to pediatric patients, but it should be noted that the autoantibody titer of children is lower than that of adults.[91] The simplified scoring system provides a moderate sensitivity, but it may be helpful in the diagnosis of pediatric AIH.[104]

Since this diagnostic scoring system was not devised for Asian countries, including South Korea, there is insufficient evidence for the association and weighting of each item with diagnosis targeting Koreans. In particular, in a single Korean study on *HLA* types among genetic predispositions, the frequency of *HLA DRB1*0405* and *DQB1*0401* was high in type 1 AIH patients, while *HLA DRB1*03* showed no association with AIH, limiting the application of the existing revised scoring system. Therefore, in the future, it is necessary to improve the items on genetic predisposition applicable to Koreans through further research on *HLA* types related to AIH in the Korean population.[16]

Overlap syndromes

AIH-PBC overlap syndrome

The "Paris criteria" is the most common and effective method to diagnose the AIH-PBC overlap syndrome.[105] It requires at least two of the following three diagnostic criteria for each disease. Two of the following three criteria for PBC should be met: (1) serum ALP level ≥2-fold the upper limit of normal (ULN) range or serum gamma-glutamyl transferase (GGT) level ≥5-fold ULN; (2) presence of AMA; and (3) a liver biopsy specimen showing florid bile duct lesions (non-suppurative destructive cholangitis of interlobular bile duct). For AIH, it requires two of the following three diagnostic criteria: (1) ALT ≥5-fold ULN; (2) serum IgG level ≥2-fold ULN or presence of SMA; and (3) a liver biopsy with moderate or severe interface hepatitis.[106] Since the revised diagnostic scoring system excludes PBC, a Korean study was performed to demonstrate that the simplified diagnostic scoring system can help diagnose overlap syndrome; however, due to the small sample size of the study, it had limited clinical application.[107]

AIH-PSC overlap syndrome

Criteria for the diagnosis of AIH-PSC overlap syndrome include the presence of typical features of AIH, absence of AMA, and evidence of large duct PSC based on bead-like appearance characterized by focal narrowing and dilatation of

Table 3. Revised original diagnostic scoring system

Feature	Score	Feature	Score
Gender		Drug history	
Female	2	Positive	-4
Male	0	Negative	1
ALP/AST (or ALT) ratio		Average alcohol intake	
<1.5	2	<25 g/day	2
1.5–3.0	0	>60 g/day	-2
>3.0	-2	Liver histology	
Serum globulin or IgG > ULN		Interface hepatitis	3
>2.0	3	Lymphoplasmacytic infiltrate	1
1.5–2.0	2	Rosetting of hepatocytes	1
1.0–1.5	1	None of the above	-5
<1.0	0	Biliary changes	-3
ANA, SMA or LKM-1 (titers)		Other changes	-3
>1:80	3	Concurrent autoimmune diseases	2
1:80	2	Additional findings	
1:40	1	Other defined autoantibodies	2
<1:40	0	*HLA DRB1*03 or DRB1*04*	1
AMA (+)	-4	Response to therapy	
Hepatitis viral markers		Complete	2
Positive	-3	Relapse	3
Negative	3		
Diagnostic scores			
Pre-treatment score		Post-treatment score	
Definite AIH	>15	Definite AIH	>17
Probable AIH	10–15	Probable AIH	12–17

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; HLA, human leukocyte antigen; IgG, immunoglobulin G; LKM-1, antibody to liver kidney microsome type 1; SMA, smooth muscle antibody; ULN, upper limit of normal range.

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Table 4. Simplified diagnostic scoring system

Feature	Value	Score
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	+2*
or LKM-1	≥1:40	+2*
or SLA	Positive	+2*
IgG	>ULN	1
	>1.1xULN	2
Liver histology (evidence of hepatitis is a necessary condition)†	Compatible	1
	Typical	2
Negative viral markers	Yes	2
Diagnostic scores		
≥6	Probable AIH	
≥7	Definite AIH	

AIH, autoimmune hepatitis; ANA, antinuclear antibody; IgG, immunoglobulin G; LKM1, antibody to liver kidney microsome type 1; SLA, antibody to soluble liver antigen; SMA, smooth muscle antibody; ULN, upper limit of normal range.
*Addition of points achieved for all autoantibodies (maximum, 2 points).
†Interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis, and hepatic rosette formation were regarded as typical for diagnosis of AIH. To be considered typical, each of the three features of typical AIH histology have to be present. Compatible features are a picture of chronic hepatitis with lymphocytic infiltration without all the features considered typical.

the bile duct on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography (ERCP), or evidence of small-duct PSC based on characteristic fibrous obliterative cholangitis on histology.[108] In a study of patients with PSC, it was reported that the revised diagnostic scoring system could help diagnose AIH-PSC overlap syndrome.[109]

[Recommendations]

1. AIH is diagnosed by excluding liver injury from other causes and integrating laboratory findings (increased serum AST, ALT, and/or IgG), the presence of autoantibodies, and compatible histologic findings. (B1)
2. If AIH is suspected, ANA and SMA are performed as screening tests. (B1) Anti-LKM1, anti-LC1, anti-SLA, or ANCA can be further examined if clinically necessary. (C1)
3. AIH can be diagnosed with a revised diagnostic scoring system or a simplified diagnostic scoring system. (B2)
4. If a patient with AIH shows a cholestatic pattern of liver function test, AMA and cholangiography should be performed, considering the possibility of AIH-PBC overlap syndrome or AIH-PSC overlap syndrome. (C1)

AIH-like drug-induced liver injury

Clinical manifestations and pathological findings of DILI caused by an unpredictable idiosyncratic drug reaction or hypersensitive drug reaction were similar to those of AIH in about 2-17% of patients reported as AIH.[110-112] The leading causative agents are known to be nitrofurantoin, minocycline, alpha-methyl DOPA, and hydralazine.[113] DILI can resemble the clinical manifestations of AIH by causing the formation of serum autoantibodies and gammaglobulinemia. A liver biopsy can be performed to differentiate between DILI and AIH. However, DILI may be difficult to distinguish from AIH due to the manifestation of interface hepatitis and plasma cell infiltration.[114] Therefore, drugs and supplements exposed before disease onset should be clearly identified. After drug exposure, the latency period of AIH-like DILI varies greatly, ranging from 1–8 weeks to 3–12 months.[21,115] Moreover, the assessment of response to and recurrence after glucocorticoid therapy is helpful in differentiating between AIH and DILI.[113]

AIH-like DILI mainly affects women, and acute hepatitis is the common manifestation of DILI in more than 60% of all cases. Cardinal symptoms include nausea, vomiting, lethargy, and right upper quadrant pain. Approximately 30% of DILI

patients display signs of drug hypersensitivity reactions, such as fever, rash, and increased eosinophils.[21] In genetic tests, *HLA DRB1*03:01* or *HLA DRB1*04:01* are found to be similar to healthy controls, and autoimmune disease is rarely accompanied.[116] When a previous study reviewed 261 patients diagnosed with AIH over a decade, AIH-like DILI was detected in 24 patients, accounting for 9.2% of all cases.[110] The median age was 53 years (interquartile range, 24–61), and nitrofurantoin and minocycline were the most common agents associated with DILI.[110] Liver enzyme levels were elevated up to 5–20 times the normal amount, while ALP increased slightly. Serum bilirubin varied to over 20 mg/dL from the normal range, and elevated gamma globulin levels, ANA positivity (83%), and SMA positivity (50%) were observed.[110] Furthermore, the symptoms were mitigated by stopping the causative drug and receiving glucocorticoid treatment. No relapse was observed after discontinuation of immunosuppressive treatment, and none of the patients progressed to LC.[110] Immune-related adverse events are being increasingly reported, with the growing use of immune checkpoint inhibitors that activates immune cells to block various cancers. DILI caused by immune checkpoint inhibitors is highly responsive to glucocorticoid therapy, and it usually shows negative or low levels of serum ANA and SMA and has normal gamma globulin levels.[117]

Monitoring is warranted to check for improvement in clinical manifestations and laboratory findings without recurrence after stopping the causative agents. Most cases of DILI improve within a month, but may rarely persist for more than 3 months. According to Hy's Law criteria, when serum AST and ALT levels are elevated more than three times the ULN and serum bilirubin is greater than two times the ULN, it leads to the risk of death or liver transplantation in approximately 9–12% of cases.[118,119] The use of glucocorticoids is considered when symptoms show no improvement despite the suspension of drug use and meet Hy's Law criteria. The diagnosis of DILI can be confirmed when normal values are maintained in routine blood tests after the withdrawal of glucocorticoid therapy. On the contrary, repeatedly elevated liver enzymes may indicate AIH. Relapsing hepatitis is managed the same way as AIH using immunosuppressive agents.[120] Most patients with AIH-like DILI have a good prognosis, but this condition may rarely result in death, in about 5%, due to idiosyncratic drug response and require liver transplantation in about 4.5% of cases.[121]

Summary

AIH-like DILI is challenging to distinguish from AIH only based on clinical manifestations, laboratory, and biopsy findings. This condition can be discriminated from AIH based on the history of medication before disease onset and no recurrence despite discontinued steroid treatment.

Non-invasive fibrosis assessment

Serum biomarkers

The degree of liver fibrosis of AIH patients can be estimated using serum panel. The serum panel including FibroTest which combines five serum biochemical markers (α-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, GGT) with patient age and gender,[122-124] aspartate aminotransferase-to-platelet ratio index (APRI),[125] Fibrosis-4 index (FIB-4) which combines patient age with measurements of 3 biomarkers (AST, ALT and platelet),[126,127] enhanced liver fibrosis test (ELF) which combines tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA),[128,129] are well-validated non-invasive tests in viral hepatitis. However, their role in predicting the progression of liver fibrosis, long-term prognosis, and development of hepatocellular carcinoma (HCC) in AIH remains unknown.[130] Another serum marker Mac-2-binding protein glycan isomer (M2BPGi) has been studied in Japanese AIH patients, but its applicability in Korean patients requires further validation.[131,132]

Imaging modalities

The ultrasound-based measurements of liver stiffness comprise transient elastography (TE), 2D shear wave elastography (SWE), and point SWE, while other methods include magnetic resonance elastography (MRE).

In AIH, studies based on FibroScan® are relatively more common than other non-invasive imaging modalities.[133-136] The median value of liver stiffness measurement (LSM) in AIH patients was higher than that of healthy controls (11.2±8.2 kPa vs. 4.3±1.4 kPa, P <0.01).[136] A robust positive correlation was observed between LSM and histological fibrosis stage.[134] However, the LSM value was higher within 3 months of treatment, and the area under the receiver operating characteristic curve (AUROC) at 6 months was higher than that at 3 months of treatment (≥F2, 0.68 vs. 0.97; ≥F3, 0.8 vs. 1.0; F4,

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0.71 vs. 1.0). The best cut-off values for ≥F2, ≥F3, and F4 at 6 months of treatment were 5.8 kPa, 10.5 kPa, and 16.0 kPa, respectively.[134] Since hepatic inflammation impacts LSM, ≥F3 can be more accurately diagnosed after 6 months of treatment when hepatic inflammation is resolved.[134] In another retrospective study, patients who failed to achieve complete biochemical remission showed a slight increase in LSM (+1.7%/year; 95% CI, -6.0% to 12.1%; *P*=0.19), while a significant decrease in LSM (-7.5%/year; 95% CI, -11% to -2.0%; *P*=0.0003) was observed in the complete biochemical remission group, indicating that fibrosis regression can be monitored by TE.[135] According to a meta-analysis, TE performed better than serum markers, FIB-4 and APRI, in staging advanced fibrosis ≥F3.[130,137]

The AUROCs for 2D-SWE in diagnosing ≥F2, ≥F3, and F4 were 0.85, 0.85, and 0.86, respectively.[138] Other studies reported similar AUROCs ranging from 0.781 to 0.84,[139,140] showing higher predictive efficacy compared to APRI and FIB-4 (AUROC, 0.84 vs. 0.57 vs. 0.63).[140] A single-center study in South Korea on point SWE which generates shear wave in one area revealed an AUROC of 0.8, similar to the results of studies from other countries that showed point SWE outperforming APRI and FIB-4.[141]

The MRE has the advantage of evaluating the whole liver, and MRE appeared to outperform TE for staging hepatic fibrosis in some studies focusing on other liver diseases.[142] One study based on 36 patients showed that the AUROCs for advanced fibrosis (≥F3) and cirrhosis (F4) were 0.97 and 0.98, respectively.[143] The best cut-off values for ≥F3 and F4 were 4.1 kPa (sensitivity 89.5%; specificity 100%) and 4.5 kPa (sensitivity 92.5%; specificity 96%), respectively, revealing a very high diagnostic accuracy.[143] Although a study comparing MRE with TE is lacking, MRE outperformed APRI and FIB-4; and therefore, further evaluation on the role of MRE in AIH patients is required in the future.

[Recommendations]

1. Transient elastography can be useful in diagnosing advanced fibrosis (≥F3) or cirrhosis in patients with AIH and should be performed after hepatic inflammation has been resolved in patients undergoing induction therapy. (C2)

TREATMENT

Treatment aims and indications

Treatment aims and definitions of treatment endpoints

The goals of AIH treatment are to minimize the risk of complications caused by drugs, control the liver inflammation, and achieve remission to suppress the progression of liver disease. To achieve these aims, long-term or permanent maintenance therapy after remission is required in most patients with AIH.

The ideal biochemical response is the normalization of serum ALT, AST, and IgG, and the ideal treatment response is the loss of histologic inflammation along with the biochemical response.[21,93,144-148] Even with the biochemical response, histologic inflammation often persists. Since aminotransferases and IgG do not reflect the activity of histologic inflammation, especially in the case of cirrhosis,[82,149] liver biopsy may be necessary to confirm the loss of histologic inflammation. A study with paired liver biopsy in 120 patients with a biochemical response for more than 6 months showed that 46% of patients had a histological activity with an Ishak score of 4 or higher, and it was an independent factor associated with death or liver transplantation.[149]

Complete biochemical response is the normalization of serum transaminases and IgG below the ULN within 6 months of treatment (Table 5).[150] Insufficient response is the lack of complete biochemical response, determined no later than 6 months after the initiation of treatment. Non-response is <50% decrease of serum transaminases within 4 weeks after the initiation of treatment. Remission refers to a case where the hepatitis activity index (HAI) of liver tissue is less than 4 out of 18 points.[150] Intolerance to treatment is any adverse event possibly related to treatment as assessed by the treating physician, leading to potential discontinuation of the drug.[21]

Persistent elevation of AST or ALT level during treatment is known to predict the progression of liver diseases and poor prognosis, such as recurrence, histological activity, cirrhosis, and hepatocellular carcinoma, after treatment is discontinued.[146-148,151,152] According to a retrospective study of 132 patients with AIH, patients whose serum biochemical indicators did not return to normal had a 3–11 times higher risk of relapse after discontinuation of treatment compared to patients with normal serum biochemistry.[146] Another study re-

Table 5. Endpoints for AIH treatment as proposed by the International Autoimmune Hepatitis Working Group after a consensus process

Endpoint	Definition
Complete biochemical response	Normalization of serum transaminases and IgG below the ULN within 6 months of treatment
Insufficient response	Lack of complete biochemical response. Should be determined no later than 6 months after initiation of treatment
Non-response	<50% decrease of serum transaminases within 4 weeks after initiation of treatment
Remission	Hepatitis activity index <4
Intolerance to treatment	Any adverse event possibly related to treatment as assessed by the treating physician leading to potential discontinuation of the drug

ULN, upper limit of normal range.

ported that only 4% of patients with normal serum biochemical indicators experienced histological deterioration, while 54.5% of patients without normalization experienced histological and clinical deterioration.[151] In addition, since serological indicators, especially ALT and IgG, are closely related to histological activity,[153] normalization of these can be used as indicators to predict histological remission.

Treatment indications

Active research on the treatment of AIH was conducted from the 1960s to the 1970s,[154-158] and treatment regimens based on the results of these studies are valid to date. Since the hepatitis C virus was discovered in 1989, there is a possibility that chronic hepatitis C patients may have been included among patients diagnosed with AIH before 1989, and therefore, some hepatitis C patients may have been included in the initial clinical trial. In a prospective randomized controlled study conducted for the first time in patients with chronic active hepatitis, the placebo group without treatment showed a high mortality rate of 56% at the 72-month follow-up, whereas the mortality rate of patients treated with prednisolone decreased to 14%.[154] In several subsequent randomized controlled studies, patients with chronic active hepatitis who were not treated showed a high mortality rate (41% at 3–3.5 years of follow-up), whereas those treated with prednisone alone or prednisone plus AZA showed a reduced mortality by 6–10%.[155,157] Accordingly, it has been confirmed that untreated active AIH has a very poor prognosis, and that appropriate immunosuppressive therapy improves liver function and increases survival.

Evidence on the natural course and benefits of immunosuppressive treatment in asymptomatic AIH patients with mild inflammatory activity is still insufficient. A Canadian single-center cohort study of 126 patients with AIH reported a 10-year survival rate of 80.0% (95% CI, 62.5–97.5%) for patients with asymptomatic AIH, and untreated asymptomatic patients showed a statistically insignificant survival difference compared to asymptomatic patients who received treatment.[22] On the other hand, in another retrospective study conducted in the United States, some asymptomatic patients with mild activity reached remission without treatment, but the rate of reaching remission was significantly lower than that of patients who received immunosuppressive therapy (12% vs. 63%, P= 0.006), and their 10-year survival rate was also significantly lower (67% vs. 98%, P <0.01).[159] AIH may have reached remission spontaneously without treatment, but the spontaneous remission did not persist after recurrence.[22,159] In a large retrospective study of 305 patients with AIH, asymptomatic patients had significantly lower biochemical and histological activity compared to symptomatic patients, but the response rate to immunosuppressive therapy (complete response rate P=0.558; nonresponse rate P=0.462) and liver-related prognosis (P=0.975) were found to be similar between the two groups.[24] If AIH is not treated, it is difficult to predict the disease course as the activity continuously changes; and a significant number of asymptomatic patients develop symptoms (25.8–69.6%),[22,160] experience liver disease progression (22.2–50%),[24,159,160] or progress to hepatocellular carcinoma, end-stage liver disease, or liver failure.[159,160] In a multicenter longitudinal cohort study in the UK, all patients with AIH treated with glucocorticoids had lower overall mortality and lower liver transplant rates compared to untreated patients (hazard ratio [HR], 0.25; 95% CI; 0.14–0.45; P <0.001); and in particular, the overall mortality and liver transplantation rates were significantly lower (HR, 0.13; 95% CI, 0.04–0.42; P=0.001) when even asymptomatic patients were treated.[161]

Considering the natural course of AIH and the effect of im-

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munosuppressive therapy, active AIH patients with abnormal clinical and laboratory findings (elevation of AST, ALT, and IgG) or liver tissue findings suggesting intrahepatic inflammation (HAI ≥4) are subject to immunosuppressive treatment. When treatment is withheld in asymptomatic inactive patients with an HAI score of less than 4 without advanced fibrosis, liver enzyme levels and IgG markers should be monitored regularly.

[Recommendations]

1. The goal of AIH treatment is to achieve remission by controlling the liver inflammation, thereby suppressing the progression and complications of liver disease. (B1)
2. Patients with active AIH should be treated with immunosuppressive therapy. (A1) When treatment is withheld in asymptomatic inactive patients with an HAI score of less than 4 without advanced fibrosis, liver enzyme levels and IgG markers should be monitored regularly. (C1)
3. In patients with AIH, serum aminotransferase levels and IgG are measured regularly to evaluate treatment response after initiation of treatment. (B1)

First-line treatments

First-line standard therapy

For the induction of remission of AIH, prednisolone 20–40 mg and AZA 50–150 mg are administered in combination daily, or prednisolone 40–60 mg alone daily (Fig. 5). Combination therapy of prednisolone at higher doses (up to 1 mg/kg/day) and AZA can induce rapid remission in patients with AIH without cirrhosis,[162] but steroid-related side effects should be taken into consideration.

The efficacy of prednisolone alone or AZA combination therapy in AIH has been demonstrated through several randomized controlled trials.[154-158] A systematic review of these randomized controlled trials showed similar remission rates between predniso(lo)ne monotherapy and AZA combination therapy (42% vs. 43%; relative risk [RR], 0.98; 95% CI, 0.65–1.47), and fewer drug-related adverse events occurred with AZA combination therapy.[163] Prednisolone and AZA combination therapy is similar in efficacy to prednisolone monotherapy, but has advantages in terms of adverse events and is preferred as the first-line treatment.[20] On the other hand, when the treatment duration is expected to be shorter than 6 months, such as AIH-like DILI, or when AZA is contraindicated, prednisolone monotherapy is recommended.[21]

According to a retrospective study on the initial dose of prednisolone, when comparing prednisolone 30 mg and 40 mg as a combination therapy with AZA, the remission rate at 3 months of treatment was higher in the 40 mg group (69.2% vs. 43.8%, P=0.031), but there was no statistically significant difference in remission rates at 6 months and 12 months (79.5% vs. 59.4%, P=0.065; 89.5% vs. 80.6%, P=0.30) and in recurrence rate during maintenance therapy (35.9% vs. 50%, P=0.23).[164] In a multicenter retrospective study conducted in Europe, there was no significant difference in biochemical response rates at 6 months between the high-dose prednisolone (≥0.5 mg/kg/day) and low-dose prednisolone (<0.5 mg/kg/day) treated groups (70.5% vs. 64.7%, P=0.61). There was no statistically significant difference in glucocorticoid-related adverse events between the two groups, but the incidence of glucocorticoid-induced diabetes (7.7% vs. 3.9%, P=0.13) and osteoporosis (6.4% vs. 2.6%, P=0.09) was higher in the high-dose administration group.[165] A meta-analysis of 25 studies on glucocorticoid doses reported that high-dose glucocorticoid (60 mg/day or 1 mg/kg/day) administration had a higher biochemical remission rate (79% vs. 72%) compared to low-dose glucocorticoids (40–50 mg/day or 0.5 mg/kg/day), but liver transplantation or mortality (3% vs. 1%) and glucocorticoid-related adverse events (42% vs. 39%) were also higher.[166]

In combination therapy for inducing remission of AIH, AZA can be administered simultaneously with prednisolone or administered sequentially with an interval of about 2 weeks. When administered sequentially, the response to prednisolone can be evaluated with prednisolone administration alone during the first 2 weeks of treatment, eliminating the uncertainty of diagnosis and accurately evaluating the treatment response by excluding AZA-induced hepatotoxicity that may rarely occur in severe liver disease.[20,167] In addition, the risk of complications can be predicted by evaluating the patient's *NUDT15* (Nudix hydrolase 15) and *TPMT* (thiopurine S-methyltransferase) gene mutations during the first 2 weeks of not administering AZA.[21] AZA is initially administered in combination with prednisolone at a dose of 50 mg/day and may be increased to 150 mg/day or 2 mg/kg/day depending on toxicity and response to treatment. If a *NUDT15* or *TPMT* gene variant is present, AZA metabolism is impaired and the risk of cytopenia due to bone marrow suppression increases.

Since patients homozygous for any risk variants have almost no enzymatic activity, prednisolone monotherapy or alternative therapy without AZA should be considered. Even the patients who are heterozygous for risk variants can also have a risk of bone marrow suppression, so the dose of AZA should be reduced. When considering a dose of 2 mg/kg/day or more, the starting dose of AZA should be reduced by 30–80% and adjusted based on the degree of myelosuppression.[168] In particular, more attention should be paid to patients with risk variants in both the *NUDT15* and *TPMT* genotypes.

If there is a biochemical response with an initial dose of prednisolone and AZA, monitoring should be conducted every 1–2 weeks and prednisolone gradually reduced to a dose that maintains the biochemical response or 20 mg/day while maintaining AZA. Then, monitoring should be performed every 2–4 weeks and prednisolone gradually reduced by 2.5–5 mg to maintain 5–10 mg/day or a dose that maintains the biochemical response. After achieving a complete biochemical response, prednisolone can be discontinued while maintaining AZA. In several randomized controlled trials of maintenance therapy,[169-171] AZA alone maintenance therapy showed a higher sustained remission rate than predniso(lo)ne alone maintenance therapy (92% vs. 68%; RR, 1.31; 95% CI, 1.07–1.70), and there was no significant difference in the sustained remission rate compared to predniso(lo)ne plus AZA maintenance therapy (92% vs. 96%; RR, 1.06; 95% CI, 0.94–1.20).[163] In addition, high-dose AZA monotherapy (2 mg/kg/

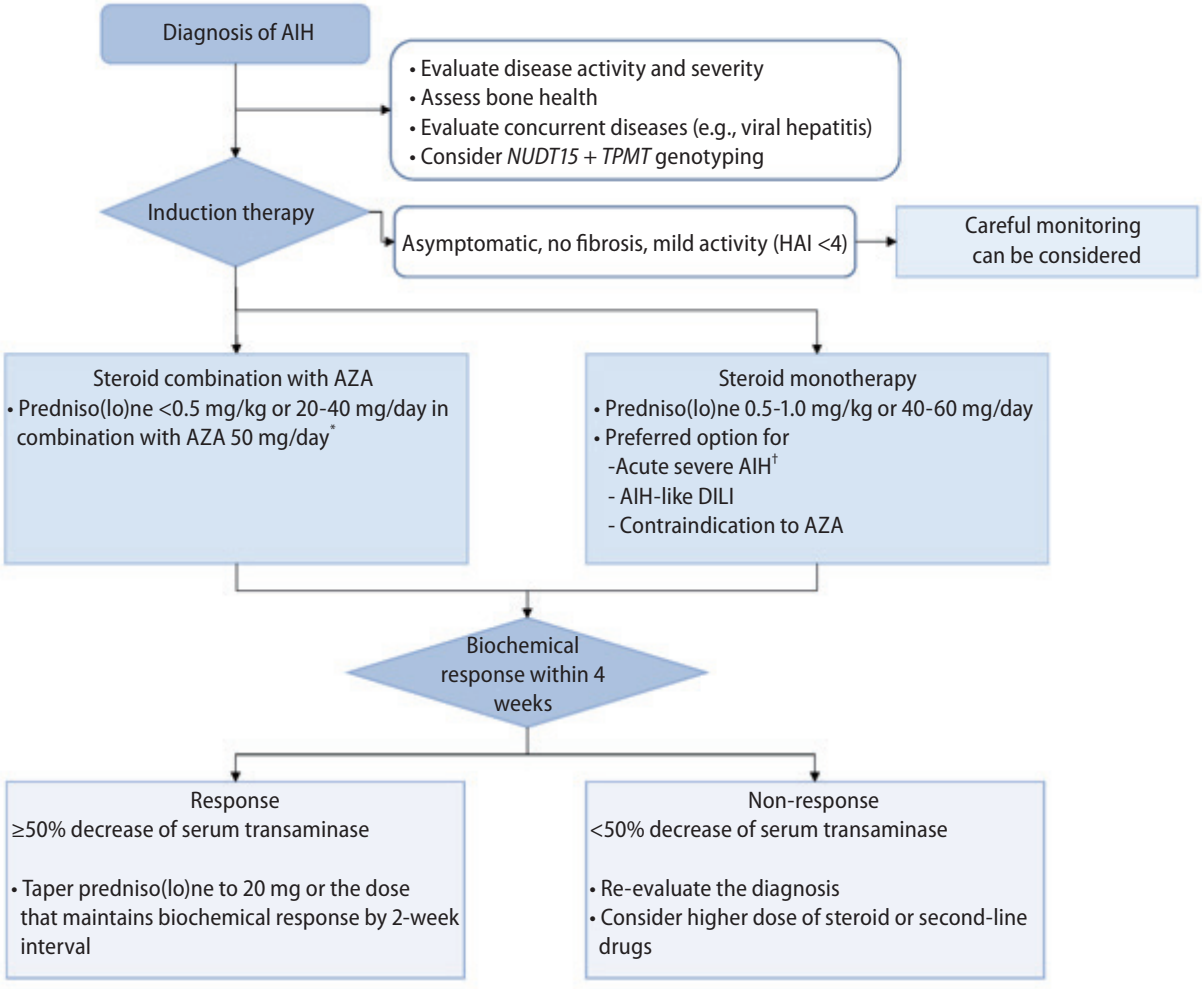

Figure 5. Induction strategy for autoimmune hepatitis. AIH, autoimmune hepatitis; AZA, azathioprine; DILI, drug-induced liver injury; HAI, hepatitis activity index; NUDT15, Nudix hydrolase15; TPMT, thiopurine S-methyltransferase. *Delayed institution of AZA by 2 weeks can be considered. †Emergent evaluation for liver transplantation should be considered for patients with ALF.

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day) reduced glucocorticoid-induced adverse events and recurrence, showing a high remission persistence rate of 83% for an average of 67 months.[170,172] If leukopenia or thrombocytopenia occurs during AZA treatment, the dose should be reduced or discontinued; especially, if cytopenia does not recover within 1–2 weeks, AZA should be discontinued. Care should be taken in patients with LC due to the high incidence of AZA-induced cytopenia.[173,174] When AZA administration is impossible due to adverse events, the lowest dose of prednisolone alone can be administered as maintenance therapy. However, long-term administration of prednisolone in doses exceeding 10 mg per day may cause frequent steroid-related adverse events. Therefore, it is recommended to administer the lowest dose of prednisolone that maintains the biochemical reaction, keeping the dose below 10 mg/day if possible.[175]

Alternative first-line therapy

According to a prospective randomized controlled study on the efficacy and safety of budesonide and AZA combination therapy, budesonide (9 mg/day) and AZA (1–2 mg/kg/day) combination therapy showed a significantly higher 6-month biochemical remission rate (60% vs. 38.8%, P=0.001) and lower side effects of glucocorticoids (26% vs. 51.5%, P <0.001) compared to prednisolone (40 mg/day) and AZA (1–2 mg/kg/day) combination therapy in patients with AIH without cirrhosis.[176] Since budesonide has a high (>90%) first-pass effect in the liver, it has fewer adverse effects caused by glucocorticoids and can be advantageous in terms of bone density in the long term.[177-179] However, budesonide bypasses the liver due to portal systemic shunt in patients with LC, which reduces the efficacy of glucocorticoids and increases glucocorticoid-induced adverse effects.[180,181] Therefore, as a first-line treatment, budesonide and AZA combination therapy can be selectively considered in patients with AIH without cirrhosis who are highly likely to have glucocorticoid-induced adverse effects, or when prednisolone administration is not possible due to adverse effects. However, as of 2022, oral budesonide cannot be used in South Korea as it is not commercially available.

If the administration of AZA is not possible, mycophenolate mofetil (MMF) can be used as an alternative first-line treatment. A single-center prospective study reported a remission rate of 71.6% when MMF (1.5–2 g/day) was administered in combination with prednisolone as the first-line treatment for AIH, and 78.2% of them maintained remission with MMF-only (1–1.5 g/day) maintenance therapy.[182] As a result of a meta-analysis of seven prospective and retrospective studies, the predniso(lo)ne-MMF combination therapy showed significantly higher normalization rates of AST, ALT (OR, 1.49; 95% CI, 1.02–2.18), and IgG (OR, 1.87; 95% CI, 1.21–2.88), and significantly lower non-response rates (OR, 0.55; 95% CI, 0.36–0.85) compared to the predniso(lo)ne-AZA combination therapy.[183] Although MMF has been proven to be effective when administered in combination with prednisolone as a first-line treatment for AIH, it is recommended as an alternative treatment to AZA due to insufficient studies to date.

Acute severe AIH and acute liver failure due to AIH

In acute severe AIH or ALF due to AIH, the efficacy and optimal dose of glucocorticoid treatment have not yet been clearly proven due to the high rate of treatment failure,[184] the possibility of delayed liver transplantation due to initial medical treatment,[185,186] and the risk of infection due to glucocorticoid administration.[187]

According to a study of 72 patients with acute severe AIH with jaundice, the treatment failure rate was as high as 18% when treated with predniso(lo)ne at a dose of 40 to 60 mg/day. The higher the serum level of bilirubin and PT, the higher the risk of treatment failure, and the higher the risk of death and emergency liver transplantation in case of treatment failure.[184] In a French single-center retrospective study of 16 patients with acute severe AIH or ALF due to AIH (63% of whom had hepatic encephalopathy, median PT INR of 5.4), 12 patients received corticosteroid therapy, 11 patients underwent liver transplantation, one patient died, and three pateints developed severe sepsis, reporting that corticosteroid treatment increased the incidence of infection without improving the prognosis.[187] Meanwhile, in a study of 32 patients with acute severe AIH without hepatic encephalopathy, all of the untreated patients required emergency liver transplantation, whereas only 43% of patients treated with corticosteroids (mean dose of 40 mg/day of predniso(lo)ne) received emergency liver transplantation (P=0.004), and the sepsis incidence and mortality were not significantly different between the two groups (11% vs. 26%, P=0.6; 22% vs. 17%, P=0.99).[188] Another study in patients with acute severe AIH also reported favorable long-term survival (97% during 5.3 years) without progression to liver failure or liver transplantation with early administration of high-dose glucocorticoids (1.5 mg/kg/day of prednisolone).[189]