REVIEW

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Autoimmune Hepatitis: 2019 Update

Atsushi Tanaka

Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease, characterized by the elevation of aminotransferases, presence of anti-nuclear antibody or anti-smooth muscle antibody, elevated immunoglobulin G (IgG), and interface hepatitis/plasma-lymphocytic inflammation based on histology. Recent epidemiological studies have indicated an increasing trend in the prevalence of AIH worldwide, especially in male patients; this trend may suggest the alteration of environmental triggers of disease onset over time. As no disease-specific biomarker or histological finding is currently available, AIH requires a clinical diagnosis, and a validated diagnostic scoring system with acceptable specificity and sensitivity has been proposed. Regarding treatment, corticosteroids and azathioprine are recommended, and in those who exhibit an incomplete response or those who are intolerant to these drugs, second-line therapy, such as mycophenolate mofetil, is considered. Overall, the long-term outcome is excellent in patients with complete biochemical responses, while life-long maintenance treatment may be required since the cessation of immunosuppressive agents frequently leads to the relapse of the disease. Acute-onset AIH does occur, and the diagnosis is very challenging due to the lack of serum autoantibodies or elevated IgG. The unmet needs include earlier diagnosis, intervention with disseminated clinical practice guidelines, and recognition and improvement of patients' health-related quality of life with the development of novel corticosteroid-free treatment regimens. **(Gut Liver 2020;14:430-438)**

Key Words: Immunosuppressive agents; Epidemiology; Environmental factors; Health-related quality of life; Clinical trial

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown etiology in which autoimmune-mediated relativities against hepatocytes are thought to play a crucial role.[1] While middle-aged women have the highest risk for developing AIH, patients in childhood or adolescence are not uncommon. The elevation of transaminases, detectable autoantibodies, such as anti-nuclear antibodies (ANA) or anti-smooth muscle antibodies (SMA), elevation of serum immunoglobulin G (IgG) levels, and interface hepatitis or plasma cell infiltration in liver histology are characteristic features of AIH.[2] However, since there is currently no specific biomarker for the diagnosis of AIH, criteria consisting of several items are used for diagnosis.[3,4] AIH responds very well to immunosuppressive drugs, and corticosteroids are the first-line treatment.[5,6] While the overall survival of patients with AIH is comparable to that of those in the general population when the treatment response is favorable, the outcome is poor in patients with more than two relapses, even with corticosteroid treatment during the clinical course.[7] In this review, we summarize recent studies in terms of the epidemiology, etiology, diagnosis, and treatment of AIH, and finally discuss the unmet needs in AIH as a future perspective.

EPIDEMIOLOGY: AN INCREASING TREND

AIH commonly affects middle-aged women, but occurrence in childhood or adolescence is observed.[8,9] Worldwide, the peak incidence of AIH is around 50 to 60 years of age, and the highest incidence was observed around 60 to 70 years in both South Korea and Japan.[9,10] Similarly to other autoimmune diseases, female preponderance is distinct in AIH, and the male-to-female ratio is around 1:4 to 1:6.

The burden of AIH appears to be increasing worldwide, and the point prevalence reported in the published literature after

Correspondence to: Atsushi Tanaka
Department of Medicine, Teikyo University School of Medicine, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8605, Japan
Tel: +81-3-3964-1211, Fax: +81-3-3964-6627, E-mail: a-tanaka@med.teikyo-u.ac.jp
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2000 is shown in Fig. 1.[8,11-18] The point prevalence of AIH is reported to be 10 to 25 per 100,000 population in European countries, and 5 to 25 in the Asia-Pacific region. Among these, epidemiological studies were serially conducted twice in Sweden and Japan.[11,18,19] Although the study design, study area, and case findings were different, the point prevalence in Sweden was 10.7 and 17.3 in 2003 and 2009, respectively, indicating a 1.7-fold increase in 6 years.[11,18] Likewise, in Japan, the prevalence of AIH was 8.7 and 23.9 in 2004 and 2016, respectively, and thus tripled over a 12-year period.[19] It is also of note that although AIH was thought to be less frequent in Asia, the point prevalence recently reported is similar to that of the rest of the world (Fig. 1).

The male-to-female ratio of the population with AIH is considered to have changed over time, indicating a relative increase in the number of male patients. In Japan, the male-to-female ratio was 1:7 in 2004 and 1:4 in 2016.[19] Similarly, other recent epidemiological studies of AIH indicate that the male-to-female ratio is approximately 1:4 to 1:6 for AIH,[8,13,17,20] which is significantly higher than that reported previously (approximately 1:9 to 1:10).

ETIOLOGY: PERSPECTIVE FROM THE INTERACTION OF GENETICS AND ENVIRONMENT

AIH is multifactorial and involves the interaction of both genetic background and environmental triggers; accordingly, environmental insult in genetically susceptible individuals may result in aberrant immunological reactions and lead to autoimmune-mediated injury to hepatocytes. Familial clustering of AIH is frequently reported, even though the risk of AIH in the family is relatively low;[21] this indicates the importance of both genetic determinants and environmental triggers. To date, numerous susceptible loci for AIH in the human leucocyte antigen (*HLA*) and non-*HLA* region have been identified, and a genome-wide association study (GWAS) in the Netherlands determined *HLA-DRB1**0301 and *DRB1**0401 to be the most relevant susceptible genotypes for AIH, while *SH2B3* and *CARD10* (genes in the non-*HLA* region) were shown to be significantly associated with AIH.[22] Nevertheless, the associations of non-*HLA* loci have not yet been confirmed by other GWAS, indicating a strong contribution of *HLA* loci to disease susceptibility. Furthermore, recent epidemiological studies have suggested a relative importance of environmental triggers.[19] As described, an increased trend of the prevalence of AIH, especially in males, has been observed worldwide. This might be explained by a better awareness and recognition of AIH among physicians, while novel environmental factors contributing to the susceptibility of AIH and shared by both Europe and Asia-Pacific areas, and both sexes, might play a more crucial role in AIH. A well-designed case-control study is warranted to seek and identify environmental triggers in lifestyle, food, and beverages, or in chemicals, antibiotics, and xenobiotics, which trigger innate and adaptive immune responses leading to a breakdown of tolerance against hepatocytes.[19]

DIAGNOSIS: A CLINICAL DIAGNOSIS

1. Presentation

In typical cases, the presentation of AIH is insidious and patients with decompensated symptoms are rather rare, while the majority of patients with AIH have an acute-onset with general fatigue or jaundice, as described below. The elevation of transaminases, detectable autoantibodies (ANA or SMA), and elevated serum IgG level are common features captured by blood testing. Besides ANA or SMA, liver kidney/microsome (LKM)-1 antibody or soluble liver antigen is occasionally detectable in AIH, and the presence of LKM-1 characterizes type 2 AIH, while detectable ANA or SMA is a feature of type 1 AIH. A liver biopsy is required for the diagnosis of AIH, and typical findings

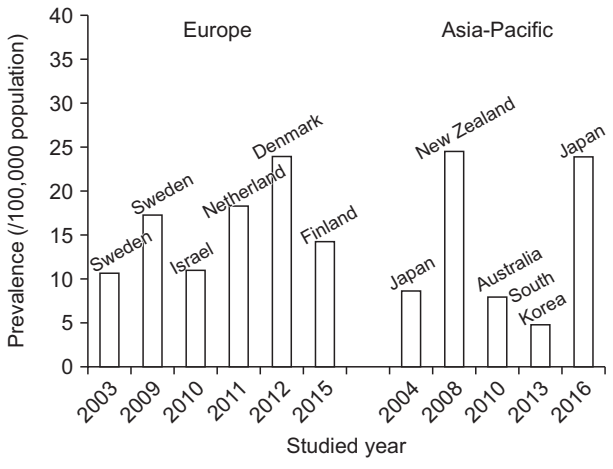

Fig. 1. The point prevalence (per 100,000 population) of autoimmune hepatitis in Europe and the Asia-Pacific region, reported after 2000.

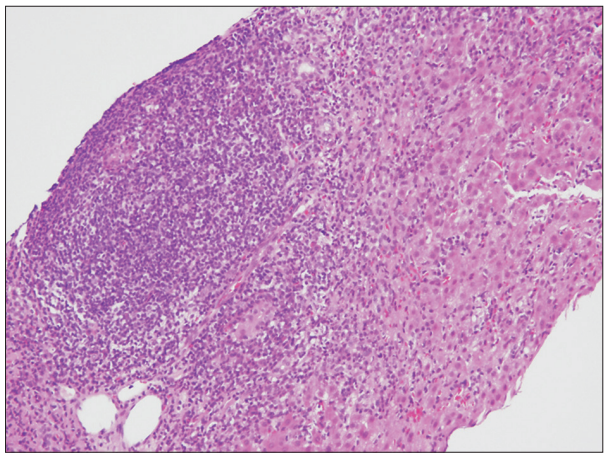

Fig. 2. Lymphocytic/lymphoplasmocytic infiltrates in the portal area and interface hepatitis; typical histological findings of autoimmune hepatitis (H&E, ×100).

of histology include interface hepatitis and lymphocytic/lymphoplasmocytic infiltrates (Fig. 2), in addition to emperipolesis, and hepatic rosette formation. However, the detection of ANA and SMA is not specific for AIH, and these histological findings are occasionally observed in other etiologies of hepatitis. Indeed, Gurung *et al*.[23] recently demonstrated that while Kupffer cell hyaline granules, prominence of plasma cells in portal tracts, and plasma-lymphocytic inflammation are significantly associated with AIH, rosette formation and emperipolesis lacked significance when compared to chronic hepatitis of other etiologies. Thus, no biomarkers with high sensitivity and specificity (such as anti-mitochondrial antibodies in primary biliary cholangitis) are available for AIH, and a combination of clinical parameters as diagnostic criteria has been used for the diagnosis of AIH.

Among a number of histological findings of AIH, liver fibrosis staging is crucial for predicting long-term outcome. Although close monitoring of fibrosis staging is essential during the clinical course, it is not feasible to carry out serial liver biopsies, and the role of noninvasive indices for fibrosis staging has been paid more attention to recently. These indices include biochemical calculation scores, such as the aspartate aminotransferase/platelet ratio (APRI) or fibrosis index based on the 4 factors (FIB-4),[24] Mac-2 binding protein glycosylation isomer,[25] magnetic resonance elastography,[26] and transient elastography.[27,28] A recent systematic review indicated that transient elastography had a good performance for determining significant fibrosis, advanced fibrosis, and cirrhosis, whereas APRI and FIB-4 showed poor performance.[29]

2. Diagnostic criteria

The diagnostic criteria for AIH were created as a diagnostic scoring system by the International AIH Group in 1993,[30] and revised in 1999.[3] This scoring system was developed for the purification of patients with AIH for clinical research and trials, and was considered too complicated for daily use. In addition, atypical AIH patients (anti-mitochondrial antibody positive AIH or anti-hepatitis C virus antibody positive AIH), who are required to be treated as typical AIH cases in daily practice, tend to be excluded by the deduction of points. Thereafter, a simplified scoring system to ease clinical application was proposed in 2008;[4] this system consisted of only four items (Table 1): Autoantibodies (ANA or SMA), IgG, liver histology, and the absence of viral hepatitis. This is user-friendly and easy to determine whether corticosteroid treatment should be commenced or not. Even though retrospective, high specificity and specificity of the simplified scoring system in the diagnosis of AIH has been validated.[31,32] A recent systematic review suggested that the simplified scoring system also provided high specificity and moderate sensitivity for the diagnosis of pediatric AIH.[33] On the other hand, in a Korean cohort of patients with AIH (n=343; mean age, 52.8 years old), definite/probable AIH according to the revised and simplified criteria were found to be 24.8%/65.4% and 34.4%/38.5%, respectively, and the concordance rate was quite low (38.8%), with modest sensitivity of the simplified criteria.[10]

Table 1. Simplified Diagnostic Criteria for AIH

Variable	Cutoff	Point
Autoantibodies	ANA or SMA 1:40	1
	ANA or SMA ≥1:80	2
	LKM (≥1:40) or SLA positive	2
IgG	>ULN	1
	>1.1×ULN	2
Liver histology	Compatible	1
	Typical	2
Absence of viral hepatitis	Yes	2

≥6, Probable autoimmune hepatitis (AIH); ≥7, definite AIH.
ANA, anti-nuclear antibodies; SMA, anti-smooth muscle antibodies; LKM, liver kidney/microsome; SLA, soluble liver antigen; IgG, immunoglobulin G; ULN, upper limit of normal.

Regarding the diagnosis of AIH, making a diagnosis of AIH after progression to a cirrhotic stage is common in both developed and developing countries. In a cohort in Pakistan and India, 84% and 71% of patients had evidence of clinical cirrhosis, respectively, with evident symptoms such as jaundice or abdominal distension.[34] Moreover, a Korean study indicated that 22.7% of patients were cirrhotic at the stage of diagnosis.[10] Even in a multicenter study in the United Kingdom, 21% of patients had clinical decompensation and/or a MELD (Model for End-Stage Liver Disease) score >15 at presentation, and delayed diagnosis (time from first abnormal liver tests to diagnosis was ≥1 year) was observed in 19% of patients.[35] It is extremely important to have a suspicion of AIH in cases with elevated transaminases and make a diagnosis of AIH at an earlier fibrotic stage, prior to progression to cirrhosis.

TREATMENT: CORTICOSTEROIDS AND BEYOND

1. Goal and indication of treatment for AIH

The aim of treatment in AIH is to achieve complete biochemical and histological remission, and prevent further progression of liver fibrosis. Complete biochemical remission is associated with the normalization of both serum alanine aminotransferase (ALT) and IgG levels. Whereas increased mortality is observed in AIH patients with cirrhosis compared to those without cirrhosis,[36] histological regression of fibrosis, as well as an improved long-term outcome will be attained by complete biochemical remission.[37,38] Although the patients with AIH who should be treated are poorly defined, those with advanced or active AIH (advanced fibrosis, cirrhosis, ALT ≥3 ×upper limit of normal [ULN]) are expected to have a poor outcome and absolute indication for treatment. On the other hand, patients with mild disease (ALT <3 ×ULN and mild or no fibrosis on histology) may not require prompt treatment, and be closely monitored until

elevation of ALT and/or IgG.[5]

2. First-line medical treatment

Immunosuppressive treatment, consisting of either corticosteroids or a combination of corticosteroids and azathioprine, has been shown to improve the long-term outcome of patients with AIH,[39] and is consistently recommended as a first-line treatment.[5,40] While the American Association for the Study of the Liver Disease guidelines recommend either prednisone monotherapy (60 mg/day) or a combination of prednisone (30 mg/day) and azathioprine (50 mg/day),[40] the European Association for the Study of the Liver (EASL) guidelines suggest 0.5–1 mg/kg/day predniso(lo)ne as initial treatment, followed by a 50 mg/day azathioprine add-on.[5] Indeed, the recommended starting dose of predniso(lo)ne, 0.5–1 mg/kg/day, is somewhat ambiguous and leaves room for variation. Recently, Pape *et al*.[41] retrospectively investigated whether a higher (≥0.5 mg/kg/day) or lower (<0.5 mg/kg/day) initial dose of predniso(lo)ne affected the rate of the normalization of transaminases, and found no significant difference between the two groups, even after adjusting clinical confounders; they concluded that the dose of predniso(lo)ne is less relevant than previously assumed.

To avoid various adverse effects of predniso(lo)ne, budesonide has been suggested as an alternative to predniso(lo)ne. Budesonide has a 90% first pass hepatic clearance rate and has less pronounced adverse effect profiles. In a prospective, double-blind, randomized trial, treatment with budesonide in combination with azathioprine for non-cirrhotic AIH patients induced biochemical remission more effectively than prednisone with azathioprine, and had a significantly lower incidence of steroid-specific adverse effects.[42] However, a case report appearing immediately after this trial, demonstrated that reactivation of AIH occurred during budesonide monotherapy and subsided with prednisone treatment.[43] In a recent retrospective study in Germany, a biochemical response was observed in 70% of patients after 12 months of treatment with budesonide monotherapy switched from prednisolone, and in 67% of patients after 24 months. At the last follow-up evaluation (63 months on average), 25% of patients received prednisolone therapy because of an insufficient response to budesonide or its side effects.[44]

3. Second-line medical treatment

In a questionnaire-based search among experts, mycophenolate mofetil (MMF) was the most frequently used a second-line treatment for AIH in the real world.[45] MMF is an ester prodrug of mycophenolic acid and is indicated for immunosuppression following organ transplant or lupus nephritis. MMF inhibits inosine monophosphate dehydrogenase, leading to the depletion of guanine nucleotides and ultimately the inhibition of DNA synthesis.[46] Although not officially approved for AIH, MMF has been shown to be effective and well tolerated in several retrospective studies of AIH patients who responded insufficiently, or were intolerant, to corticosteroids. For instance, Efe *et al*.[47] retrospectively collected data from 121 patients who received MMF as a second-line therapy, and found a complete response rate in 91.9% and 34% in corticosteroid-intolerant and insufficient responders, respectively. Recent systematic reviews demonstrated the overall efficacy of MMF as second-line therapy in AIH, with a low discontinuation rate due to side effects.[48,49] Other second-line treatments used by experts include tacrolimus and cyclosporine, and sirolimus, infliximab, and rituximab.[45]

Since B-cells play a significant role in the pathogenesis of AIH, B cell depletion is a promising strategy for the management of AIH. Ianalumab (VAY736) is a B cell activating factor receptor-blocking, monoclonal antibody that works as a B cell-depleting agent, and a clinical trial for primary Sjögren syndrome revealed therapeutic benefits without major side effects.[50] Currently, a global, prospective, randomized phase 2/3 trial is being conducted for patients with AIH who exhibited an insufficient response, or were intolerant, to corticosteroids (ClinicalTrials.gov. NCT03217422).

4. Withdrawal of immunosuppressive agents

It is well known that the long-term administration of predniso(lo)ne frequently accompanies a variety of adverse effects, including osteoporosis, exacerbation of diabetes, cataracts and glaucoma, psychosis, cosmetic changes, and malignancy. Azathioprine, considered to be less toxic than corticosteroids, has a potential to lead to the development of leukopenia and thrombocytopenia, and in some cases, malignancy. In this regard, cessation of immunosuppressive drugs should be considered after achieving clinical remission. In line with this, remission of AIH should be strictly defined and maintained for an extended period. Remission of AIH is defined biochemically and histologically; biochemical remission consists of normalization of serum transaminases and IgG, and histological remission involves the disappearance of interface hepatitis, usually achieved long after serological remission. Even if both serum transaminases and IgG are normalized, residual interface hepatitis is often still present, resulting in relapse of AIH after cessation of treatment. Therefore, clinical practice guidelines recommend that treatment should be continued for at least 3 years, and for at least 2 years after complete normalization of serum transaminases and IgG levels.[5] Thereafter, termination of therapy can be considered, but close observation with frequent testing of liver enzymes is required since relapse frequently occurs after withdrawal of immunosuppressive treatment (50% to 90%) and is typically observed in the first 12 months after withdrawal. When relapse of AIH occurs, treatment regimens correspond to initial treatment protocols with predniso(lo)ne and/or azathioprine, and are equally effective. However, it kept in mind that patients who relapse more than twice have a significantly worse outcome than those without relapse.[7] In this regard, life-long treatment with maintenance doses of immunosuppressive drugs

(predniso(lo)ne 5 mg/day and/or azathioprine 50–100 mg/day) is an alternative option to avoid disease relapse, with intensive care for side effects.

5. Liver transplantation

AIH patients with end-stage liver disease or acute liver failure who are unable to be saved with current medical treatment require liver transplantation (LT). Although data regarding LT in patients with AIH are limited, the overall survival rate in AIH appears to be excellent in AIH: The 5- and 10-year recipient survival rates are 76% to 79% and 67% to 75%, respectively, which are better than for most other indications for LT (Table 2).[51-53] On the other hand, recurrence of AIH in the graft after LT is common, and it is very challenging to determine the incidence of recurrent AIH, which is reported to be in the range of 7% to 42% (Table 2).[54-64] The inconsistency among studies is likely due to differences in diagnostic criteria, histological analysis (protocol or event-driven biopsy), small sample size in each study (no study with more than 100 patients enrolled), and follow-up time.[65,66] The rate of recurrence increases as the follow-up time increases after LT.[55,61,62] Neither the revised criteria,[3] nor the simplified criteria,[4] are validated for the diagnosis of recurrent AIH.

A number of factors are reported to be associated with the recurrence of AIH, including the severity of pre-transplant AIH[54,61] and withdrawal of corticosteroids.[59,62] HLA locus mismatching was identified as a risk factor for recurrence[67] in one study but not in others.[59-61,64] A recent study from the United Kingdom demonstrated that the 5- and 10-year recurrence rates after LT were 6% and 11%, respectively, in their cohort consisting of 69 patients with AIH, in which 87% of patients were under long-term maintenance treatment with corticosteroids after LT.[58] Compared to the recurrence rate of 27% in their previous report in 1999 in patients without long-term corticosteroid therapy,[59] the authors concluded that long-term corticosteroid use in combination with immunosuppressive agents was associated with a lower frequency of recurrence.

In general, progressing to cirrhosis and graft failure requiring re-transplantation is uncommon, even when AIH recurs in the graft.[65] However, the mechanisms that cause recurrent AIH after LT remain unclear. Furthermore, there are also substantial differences between adults and pediatric patients with *de novo* AIH, which substantiates the need for more precise diagnostic guidelines in this area.[68,69] When recurrence occurs in the graft, the strength of immunosuppression should be reinforced with re-administration or dosing-up of corticosteroids, or the addition of other immunosuppressive agents.

Table 2. Incidence and Risk Factors of Recurrence of AIH after LT

Center sites	Time period	Year	No.	Incidence	Time to recurrence, yr
Madrid, Spain[62]	1988–1996	1998	27	9 (33)	2.6±1.5
Birmingham, UK[59]	NA	1999	47	13 (28)	2.4 (0.5–5.3)
Paris, France[63]	1985–1992	1999	15	3 (20)	1.6 (1–2.5)
New York, US[64]	1988–1995	2000	24	6 (25)	1.3±0.2
Boston, US[54]	1983–1998	2000	12	5 (42)	NA
Rochester, US[57]	1985–1998	2001	41	7 (17)	4.6±1
Dallas, US[60]	1984–1998	2002	55	11 (20)	NA
Paris, France[56]	1985–1992	2003	17	7 (41)	2.5±1.7
Colorado, US[55]	1988–2006	2008	66	23 (34.8)	4.3
Alberta, Canada[61]	NA	2009	46	11 (24)	4±1.3
Birmingham, UK[58]	1999–2014	2016	69	5 (7)	3.8 (1.5–7.3)

Data are presented as number (%), mean±SD, or median (range).
AIH, autoimmune hepatitis; LT, liver transplantation; NA, not available.

Table 3. Characteristics of Acute-Onset AIH

Approximately 25%–46% of AIH
A continuous spectrum from "genuine" acute hepatitis to acute exacerbation of chronic hepatitis
Frequently ANA seronegative and/or normal IgG
Liver histology is crucial for diagnosis; centrilobular necrosis, lobular and perivenular necroinflammatory activity
Corticosteroids as effective as in classic AIH

AIH, autoimmune hepatitis; ANA, anti-nuclear antibodies; IgG, immunoglobulin G.

SPECIAL PRESENTATIONS: ACUTE-ONSET AIH

AIH could develop as an acute form, severe hepatitis, or acute liver failure (ALF) (Table 3). The definition of acute-onset AIH has not yet been strictly determined, and therefore the prevalence of acute-onset AIH varies depending on the definition and cohort. The EASL Clinical Practice Guidelines state that approximately 25% of AIH patients present with an acute-onset;[5,70] in a Korean cross-sectional study 46.4% of all AIH cases were acute-onset, defined as the presence of recent-onset symptoms (≤30 days).[10] Another recent Italian cohort demonstrated that 43% of AIH patients met the criteria of acute-onset, defined as >10 ×ULN of transaminases and >5 mg/mL of bilirubin.[71] On the other hand, the frequency of acute hepatitis was almost 11% in a Japanese nation-wide, cross-sectional study, when histological diagnosis was employed for the diagnosis of acute hepatitis.[9] It is of note that this lower number indicated the frequency of histologically determined "genuine" acute hepatitis, but did not include acute exacerbation of chronic hepatitis. Acute-onset AIH may contain two different clinical entities; acute exacerbation of chronic AIH and genuine acute-onset AIH without any chronicity. But liver histology is dynamically changing during disease process and it could be extremely challenging to differentiate these two conditions even with an experienced pathologist.

It is important to note that acute-onset AIH frequently lacks the typical serological findings of AIH, such as positive autoantibodies or elevated serum IgG. A Japanese case series involving 86 patients with acute-onset AIH disclosed that 27% patients with acute-onset AIH were ANA negative (<1:40), and there was no elevation of serum IgG in more than 50% of cases.[72] As a result, when encountering AIH patients with elevated transaminases but who lack serological diagnostic markers, the possibility of AIH is not commonly considered by physicians. This can easily lead to a delayed diagnosis and treatment, and progression to severe hepatitis or ALF; therefore, a liver biopsy is crucial for making a diagnosis of acute-onset AIH. Unlike classic and chronic AIH, centrilobular necrosis rather than portal inflammation appears to be characteristic of acute-onset AIH.[73-75] However, a recent histological study of acute-onset AIH demonstrated that this type of AIH could represent the entire spectrum of liver histology from acute hepatitis to chronic hepatitis with various activity and levels of fibrosis, and that there were no pathognomonic features for acute-onset AIH.[76] According to this study, several histological findings, including lobular and perivenular necroinflammatory activity, pigmented macrophages, and a cobblestone appearance of hepatocytes, in addition to those present in classic AIH may be beneficial for pathological diagnosis.

Regarding the treatment of acute-onset AIH, corticosteroids appear to be similarly effective as in classic AIH, without significant adverse effects.[71,72,75,77,78] The prompt initiation of high-dose intravenous (i.v.) corticosteroids (1 g methylprednisolone for 3 consecutive days followed by i.v. 1 mg/kg/day prednisolone or i.v. 1.5 mg/kg/day prednisolone) appears to be safe and may prevent progression to liver failure in patients with acute-severe AIH.[79] A recent retrospective study from India suggested that use of corticosteroids for acute-on-chronic liver failure (ACLF) with AIH as an acute insult was significantly associated with a shorter intensive care unit stay and improvement in the 90-day survival rate, while the incidence of sepsis was comparable to patients that were not treated with corticosteroids.[80] The revised Asian Pacific Association for the Study of the Liver consensus recommendations for ACLF indicate that "diagnosis of ACLF-AIH requires liver biopsy (transjugular route preferred)," and "corticosteroid therapy should be considered for a select group of patients presenting with ACLF-AIH."[81] LT is a single option for very severe cases who cannot be saved with medical treatment alone, but the optimal timing of LT is difficult to determine.[82]

FUTURE PERSPECTIVE

Whereas the long-term outcome of patients with AIH is excellent and comparable to those in the general population, several unmet needs still remain to be addressed. First, early diagnosis of the disease and treatment intervention with immunosuppressive agents should be standardized globally, especially in Asia-Pacific regions where viral hepatitis is endemic and AIH is believed to be rare. As described, more than 70% of patients with AIH were diagnosed after progression to cirrhosis in South Asia, and 20% to 25% in Korea and the United Kingdom. Furthermore, a cross-sectional study in the United Kingdom demonstrated that the current treatment regimen is not uniform (29 treatment regimens were reported among 1,249 patients in secondary care units), and as a result, the remission rates were just 59%.[83] Therefore, it is crucial to widely disseminate clinical practice guidelines for the management of AIH, making it possible to diagnose the disease at an earlier stage and to properly manage with a standardized treatment policy.

Second, the health-related quality of life (HrQOL), another important endpoint of treatment, should be carefully considered. Several studies indicated that the HrQOL of AIH patients was severely impaired and that depression appears to be a dominant symptom affecting well-being, despite clinical and biochemical features also being present.[84-86] In particular, the use of corticosteroids are significantly associated with a decreased HrQOL,[85,86] and the use of budesonide appears to improve the HrQOL.[84] These observations highlight the unmet need for an alternative treatment regimen without corticosteroids, not only for improving the long-term outcome in those who exhibit incomplete responses or who are intolerant to corticosteroids, but also for patients who demonstrate an excellent response but who also require long-term maintenance therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Atsushi Tanaka https://orcid.org/0000-0002-6358-5283

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