Similarities and Differences in Autoimmune Hepatitis Epidemiology between East and West: Autoimmune Hepatitis in East Asia, Southeast Asia, and South Asia

Hirayuki Enomoto Shuhei Nishiguchi

Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

Keywords

Autoimmune hepatitis · Prevalence · East Asia · Human leukocyte antigen DR4 · Herbal medicines

Abstract

Background: Autoimmune hepatitis (AIH) is a relatively rare disease that can develop regardless of age or ethnicity. However, its clinical features differ between eastern and western populations due to several heterogeneous genetic and environmental factors. We herein report the clinical characteristics of AIH patients in East Asia, Southeast Asia, and South Asia. **Summary and Key Messages:** The prevalence of AIH in eastern countries is considered to be lower than in western countries. Although a few young patients with type 2 AIH have been observed in South Asia, most patients in Asia are middle-aged women with type 1 AIH who respond well to steroid-based immunosuppressive therapy. Human leukocyte antigen DR4 is suggested to be an influential factor in the genetic background of AIH patients in Asia, particularly in East Asia. Notably, AIH may be induced by some societal- or culture-associated medicines, including herbal medicines. The IAIHG (International Autoimmune Hepatitis Group) scoring systems are generally accepted as the standard diagnostic methods for AIH in Asian countries. The re-

sults of repeated nationwide surveys in Japan suggest that the clinical features of AIH patients in East Asia are changing, with IgG levels and rates of anti-nuclear antibody positivity decreasing.

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Introduction

Autoimmune hepatitis (AIH) is a liver disease caused by T cell-mediated autoimmune responses to hepatic tissue, particularly targeting hepatocytes [1–8]. Several genetic and environmental factors (human leukocyte antigen [HLA] loci, viral infections, and drugs) are suggested to be associated with the development of AIH. Additionally, recent basic studies have suggested several possible mechanisms. For instance, the programmed death 1 (PD-1) and its ligand system (PD-1/PD-Ls system) act as a negative regulator of T cell signaling [9, 10]. Inhibition of the PD-1/PD-Ls system promotes an immune response, resulting in both clinical benefits (e.g., increased antiviral effects and antitumor effects [11, 12]) and drawbacks (e.g., development of various autoimmune diseases, including AIH [10]). However, thus far, the concrete causal factors of AIH have been poorly described.

Fig. 1. Clinical presentations of autoimmune hepatitis (AIH). Blue bars, green bars, and red bars correspond to East Asia, Southeast Asia, and South Asia, respectively. For reference, additional data reported from some non-Asian countries are also shown as yellow bars. There were no obvious interregional differences in the rates of acute presentation at AIH onset (**a**) or in the remission rates

with corticosteroid-based immunosuppressive therapy (**b**). **c** Reports from South Asian countries show markedly high rates of cirrhotic patients at diagnosis (India and Pakistan). Notably, the frequencies of both acute presentation and cirrhosis are low in Japanese AIH patients at diagnosis (see the Clinical Presentation heading in the Epidemiology section).

Although AIH typically develops in middle-aged women, the disease can affect all ages and all populations regardless of race and ethnicity. Patients with AIH show various clinical features, ranging from asymptomatic liver enzyme elevation to acute hepatic damage (rarely leading to acute liver failure). However, a majority of patients have chronic hepatitis with nonspecific presentation, such as general fatigue, appetite loss, and lethargy. Unfortunately, patients without obvious symptoms are sometimes left untreated, resulting in the presence of liver cirrhosis at the time of diagnosis. In severe cases, even at the first visit to a hospital, patients show clinical symptoms related to decompensated cirrhosis, such as hemorrhaging of esophagogastric varices, ascitic fluid collection, and hepatic encephalopathy. Even in the absence of clinical findings specific to AIH, AIH can cause elevated levels of aminotransferases and γ -globulin (and/or IgG). Additionally, AIH patients frequently have autoantibodies and are complicated by other autoimmune diseases [1–8].

AIH is classified into 2 types according to the autoantibody positivity. Type 1 AIH is positive for anti-nuclear

(ANAs) and/or anti-smooth muscle (ASMAs) antibodies and develops in adults and children. Type 2 AIH is positive for anti-liver kidney microsomal type 1 or anti-liver cytosol type 1 antibodies and mainly affects infants. The standard care of AIH is steroid-based immunosuppressive therapy with or without azathioprine. The initiation of treatment with corticosteroids alone and subsequent azathioprine therapy is currently recommended in order to reduce the dose of steroids administered [3].

In Asian countries, perhaps because of the high prevalence of viral hepatitis, AIH has not been well studied; however, in recent years, several papers describing the clinical features of AIH in eastern countries have been published [7, 8]. This article reviews the clinical features of AIH in Asia at present, mainly focusing on East Asia. Among Asian countries, only Japan has conducted repeated nationwide surveys of AIH patients [13–16], and clinical data from nationwide surveys were unavailable from other countries. Therefore, as a representative East Asian country, we also discuss the changing clinical features of AIH patients and the current clinical guidelines in Japan.

Table 1. Clinical characteristics of patients with AIH

Country	Patients, <i>n</i>	Type 1 AIH	Male:female	Age at onset, years	Ref.
East Asia					
Japan	1,056	93.8% ^a	1:6.0	59.9±14.7	[16]
Taiwan	48	100% ^b	1:3.4	59.8±14.2, 58.5 (21–84)	[23]
Korea	343	97.4%	1:7.3	52.8 (19–87)	[24]
China	173	≥90.2% ^c	1:6.8	53 (18–74)	[25]
Southeast Asia					
Singapore	24	91.7% ^d	1:11	Mean: 57, median: 63	[21]
Brunei Darussalam	19	100% ^b	1:3.75	52 (33–70)	[22]
Thailand	50	n.a.	1:6.1	62 (29–85)	[40]
South Asia					
India	125	71.2%	1:1.8	45.45±16.15; 46 (8–79)	[26]
Pakistan	58	62.0%	1:1.5	14.5 (4–70)	[27]
Europe and North America					
Denmark	1,721	n.a.	1:2.6	Incidence peak: around 70	[17]
UK	245	≥73.9% ^c	1:5.0	56.1 (2.5–87)	[29]
Italy	163	76.7%	1:4.6	36±21 ^e	[30]
Canada	125	≥72.0% ^c	1:3.1	43.5±16.6	[31]

^a Estimated data based on the text; ANA positive (89.1%: 886/994), ANA negative and ASMA positive (4.7%: 47/994). ^b In this study, all AIH patients were diagnosed as having type 1 AIH. ^c Estimated data based on the text concerning ANA-positive patients. Although the number of ANA-negative and ASMA-positive patients was not described, they may increase the rate. ^d Estimated data based on the text; ANA and/or ASMA positive (91.7%: 22/24). The remaining 2 patients who tested negative for ANA and SMA were also anti-LKM negative. ^e Type 1 AIH (125 patients): 42 ± 20 years, and type 2 AIH (38 patients): 15 ± 10 years.

Epidemiology

Prevalence and Incidence

AIH is a relatively rare disease of unknown cause with an increasing incidence; however, its prevalence and clinical features differ according to ethnicity. In Europe, the prevalence of AIH was estimated as 15–25 cases/10⁵ persons, increasing in both genders with time [3]. A recent nationwide study in Denmark reported an annual incidence of 1.68 cases/10⁵ persons (almost doubled during the study period: 1994–2012), and the prevalence rose to 24 cases/10⁵ persons in 2012 [17]. Regarding reports from other geographical areas, the highest prevalence of AIH was reported in Alaska in North America (42.9 cases/10⁵ persons) [18]. In Oceania, a high prevalence was reported in New Zealand (24.5 cases/10⁵ persons) [19], whereas the prevalence in Australia was not very high (8 cases/10⁵ persons) [20]. Overall, the prevalence in Oceania seems not to be lower than that in Europe or North America.

Few Asian population-based studies have examined the prevalence and incidence of AIH, but a study from Singapore [21] reported that the overall prevalence of AIH was approximately 4 cases/10⁵ persons (3, 8, and 7

cases/10⁵ persons for the Chinese, Malay, and Indian populations, respectively). Another study from Brunei Darussalam [22] showed a prevalence of 5.61 cases/10⁵ persons (4.64 cases/10⁵ persons for Malay, 12.97/10⁵ persons for Chinese, and 6.03/10⁵ persons for indigenous people). In Taiwan, the annual incidence of AIH was reported to be very low (0.52 cases/10⁵ persons) [23]. Generally, AIH is suggested to be less frequent in Asian countries than in western countries, although we cannot deny the possibility that AIH is simply underrecognized in Asia, as many physicians in Asia tend to have less interest in AIH than in viral hepatitis.

Clinical Presentation

Table 1 and Figure 1 show the clinical presentations of AIH patients, focusing on East Asia, Southeast Asia, and South Asia. Interestingly, the presence of interregional differences in patient characteristics has been suggested.

In East Asian countries, over 90% of patients have type 1 AIH, and middle-aged females are mainly affected [16, 23–25]. The rate of female patients is much higher (3.4- to 7.3-fold) than that of males. Liver cirrhosis was observed in 6.4–35.4% of patients at diagnosis in East Asian countries (Fig. 1). The frequencies of acute presentation dif-

ferred by country, being low in Japan and moderate in Korea and Taiwan. One point of note is that the incidence of cirrhosis or acute presentation at diagnosis is quite low in Japan. However, careful attention should be paid to the fact that Japan is a unique country where many citizens receive regular checkups, including liver functional tests. Easy access to health care services may therefore help identify mild cases and reduce the rate of diagnosis with evident clinical symptoms compared to cirrhosis or acute hepatitis.

In South Asian countries, type 2 AIH is relatively prevalent (11.2% in India [26] and 17.2% in Pakistan [27]), resulting in a lower frequency of type 1 AIH than in East Asian countries (Table 1). However, pediatric patients were only surveyed in Japan, India, and Pakistan. Therefore, detailed comparisons of the type 2 AIH prevalence between South Asia and other Asian regions (East Asia and Southeast Asia) are not easy. However, compared with the findings of a nationwide survey of Japanese patients, the average age of affected individuals in South Asian countries is relatively young, and AIH patients in South Asia are suggested to have a number of unique clinical features. Although the presence of young patients in the study population may have contributed to the high frequency of type 2 AIH in South Asia, most pediatric patients with AIH in Singapore suffer from type 1 AIH, just as adult patients [28]. Therefore, the relatively high frequency of type 2 AIH should be taken as a characteristic finding of South Asian patients, independent of the age at onset.

As another feature differentiating South Asians from East Asians, the percentage of female patients was relatively low, although the rate of occurrence in females was still higher than in males (1.8-fold in India and 1.5-fold in Pakistan). Additionally, liver cirrhosis was frequently observed at diagnosis in South Asia (71.2% in India [26] and 84.1% in Pakistan [27]). On comparison with AIH patients in non-Asian countries [17, 29–31], the frequencies of cirrhotic patients at diagnosis were markedly high in South Asia (Fig. 1).

In brief, the distinctive features of South Asian AIH patients are as follows: relatively high incidence of type 2 AIH, affecting both adults and children; relatively low incidence in females and presence of advanced liver disease at diagnosis. In Southeast Asian countries, middle-aged females were predominantly affected with type 1 AIH. Despite the lower rate of cirrhosis at diagnosis in East Asia compared to South Asia, the other clinical features of AIH in Southeast Asia were generally similar to those in East Asia (Fig. 1; Table 1).

Regarding the treatment response, patients in Asian countries usually respond well to corticosteroid-based immunosuppressive therapies (Fig. 1). Patients in East Asia and Southeast Asia showed particularly high response rates, ranging from 70 to 93%. Despite the fact that relatively few reports have been conducted in South Asia, a report from India showed a 70.5% remission rate. In addition, another paper from India [32] reported a remission rate of 71.0%. These reports suggest that patients in South Asia should respond to immunosuppressive therapies above a certain rate.

Genetics

The abovementioned interregional differences in the clinical features of Asian AIH may be due in part to genetic variations, as the genetic backgrounds differ among Asian populations. East Asian persons mainly have Mongoloid ancestry, and Southeast Asian persons have both Australoid and Mongoloid ancestry. South Asian countries are influenced by a number of ancestries, including Caucasoid in addition to Australoid and Mongoloid. A recent genome-wide study further revealed that the genetic sources of South/Central Asian populations differ from those of East Asians [33]. These genetic differences may contribute to the varied clinical presentations of AIH among East Asia, Southeast Asia, and South Asia.

While the genetic factors determining the susceptibility to AIH have not been fully clarified, the highly polymorphic HLA complex is suggested to be significantly associated with the development of AIH. Regarding patients in Europe and North America, the HLA-DRB1 locus, particularly HLA-DR3 (DRB1*0301) and DR4 (DRB1*0401), is a genetic characteristic likely related to susceptibility to type 1 AIH [34, 35], and significant associations between this locus and susceptibility to AIH were demonstrated by a recent genome-wide study (HLA-DRB1*0301, $p = 5.3 \times 10^{-49}$ and HLA-DRB1*0401, $p = 2.8 \times 10^{-18}$) [36]. In that study, polymorphisms of non-HLA genes, including Src homology 2 adaptor protein 3 (SH2B3) and caspase recruitment domain family member 10 (CARD10), were also identified as disease susceptibility genes ($p = 7.7 \times 10^{-8}$ and $p = 3.0 \times 10^{-6}$, respectively). However, dominant disease-related genes vary by population; for example, HLA-A2, HLA-B8, and HLA-C7 (63%) have been regarded as more important genetic characteristics of AIH patients than HLA-DR3 and HLA-DR4 in German patients [37]. The genetic susceptibilities

also differ between first nations and non-first nations in the US [38].

Regarding East Asia, HLA-DR4 is common in Japanese AIH patients, while HLA-DR3 is rare. In 898 Japanese patients, HLA-DR4 was detected in 22.4% of cases and considered to be the disease susceptibility gene, whereas HLA-DR3 was observed in only 0.2% of cases [35]. However, it should be noted that unlike in westerners, HLA-DR4 (DRB1*0405, but not DRB1*0401) is considered to induce disease-susceptibility in Japanese patients. Similarly, HLA-DR4 (DRB1*0405) was also suggested to be a disease susceptibility gene in Chinese patients [35]. In Korea, HLA-DR3 and HLA-DR4 are suggested to be involved in the susceptibility to AIH, but HLA-DR4 was more frequently observed than HLA-DR3 [35, 39]. In Taiwan, HLA-DQ5 (50%), HLA-CW7 (50%), HLA-A11 (55%), and HLA-DR4 (36%) were frequent in AIH patients [23].

Regarding Southeast Asia, in a report from Thailand [40], only HLA-DR3 (DRB1*0301) was significantly associated with AIH. In Brunei Darussalam [22], in addition to HLA-DR3 (DRB1*03) and HLA-DR4 (DRB1*04), HLA-Cw7 and HLA-DQB1*04 had significantly higher frequencies in AIH patients than in controls ($p = 0.038$ and $p = 0.007$, respectively).

Regarding South Asia, few studies have examined the genetic factors associated with AIH. In one study from Pakistan [27], HLA-A2, HLA-A9, HLA-A10, HLA-A19, HLA-B15, HLA-B40, and HLA-DR6 were reported as potential disease-related genetic characteristics. These authors reported that HLA-DR6 was the most strongly related factor; however, its clinical significance remains unclear and needs to be further evaluated. Taken together, these reports showed the absence of defining genetic characteristics in Asian AIH patients. However, HLA-DR4 seems to have clinical influence in Asian patients, at least in East Asian countries such as Japan and China.

In patients with HLA-DR4, AIH mainly develops in middle-aged persons with mild disease severity, whereas in patients with HLA-DR3, AIH frequently develops in relatively young persons as a treatment-resistant disease [1, 35]. The disease susceptibility of HLA-DR4 is consistent with the clinical features of Japanese patients, with a majority of cases occurring in elderly patients and with a high response rate to immunosuppressive treatment [16, 35]. Furthermore, the high frequencies of HLA-DR4 in East Asian patients may also partially explain the onset at older age and favorable treatment responses in patients in that area.

Environment and Nutrition

AIH is suggested to be induced by several environmental factors, including viral infections and drug administration. Several viruses, including hepatitis A virus [41], hepatitis B virus [42], hepatitis C virus [42, 43], hepatitis E virus [44], Epstein-Barr virus [45], and human herpes viruses [46, 47] are reported to have a possible relationship with the development of AIH.

Medical drugs are also reported to be associated with the induction of AIH. Two anti-infective agents – nitrofurantoin and minocycline – are well-known causes of drug-induced AIH, totally accounting for about 90% of reported cases of drug-induced AIH [48, 49]. However, various categories of medical drugs, such as antihypertensive agents, nonsteroidal anti-inflammatory agents, immunomodulatory agents (interferons and anti-TNF- α agents) and, have also been reported to be associated with the onset of AIH [48–50]. In 2011, Czaja [50] summarized 33 drugs suggested to be associated with the induction of AIH, including not only common medical drugs but nutritional supplements, herbal medicines, and 1 environmental pollutant. In that review article, the only articles from Asian countries were 2 Japanese papers reporting cases treated with minocycline [51] and *dai-saiko-to* (herbal medicine) [52].

Because of the low number of reports, the environmental and nutritional factors related to drug-induced AIH in Asian countries have not been sufficiently clarified. However, the number of reports from Asia regarding drug-induced AIH has increased in recent years. From Japan, Sugimoto et al. [53] reported 7 cases of drug-induced AIH, including 2 induced by anti-infective agents, 2 by herbal remedies, 2 by nonsteroidal anti-inflammatory agents, and 1 by a uricosuric agent. More recently, Hisamochi et al. [54] reported 62 patients diagnosed with drug-induced liver injury, including 23 cases with AIH-like histological findings. Among these 23 cases, 16 received complementary alternative medicines including dietary supplements and herbal medicines. A paper from Korea also suggested a relationship between the administration of herbal medicines and AIH development [55]. In a report from India with 125 AIH patients, a drug history was observed in 19 patients, and most of them had received indigenous Ayurvedic agents or anti-tuberculosis agents [26]. These reports suggest that some culture- or region-associated medicines such as herbal medicines may be involved in the occurrence of AIH in Asian countries. Additionally, complementary and alternative medicines may become

relevant in clinical practice in western countries, since the use of such medicines has been increasing in many countries [56].

Diagnosis

Two scoring systems have been proposed by the International Autoimmune Hepatitis Group (IAIHG): the revised international diagnostic criteria [57] and the simplified international diagnostic criteria [58]. These well-recognized criteria are commonly used for the diagnosis of AIH in Asian countries. However, the clinical features of AIH are heterogeneous, and additional diagnostic criteria for Japanese patients have also been proposed with respect to the findings of a nationwide survey in 1996 [59]. Decades later, in response to changing clinical manifestations among Japanese AIH patients, new diagnostic criteria were proposed in 2013 [60]. However, these criteria alone cannot provide an accurate diagnosis, and the 2 globally approved IAIHG scoring systems are concurrently used in Japan (see the Guidelines section). Overall, despite the presence of original diagnostic criteria in Japan, the IAIHG scoring systems remain standard diagnostic tools of AIH in Asian countries.

Guidelines

Changes in the Clinical Characteristics of Japanese AIH Patients

The clinical aspects of AIH vary depending on genetic and environmental factors. For instance, as described above, HLA-DR-3 is quite rare in Japanese AIH patients. In addition, the recently identified disease-related gene CARD10 was unlikely to be associated with susceptibility in Japanese patients with type 1 AIH [61]. These findings suggest that an original guideline for eastern countries is warranted. However, no specific guidelines for managing all Asian AIH patients have yet been established.

Japan is unique among East Asian countries, as nationwide surveys for AIH have been sequentially conducted, and the results of the latest analysis were reported in 2011 [16]. Earlier surveys [13–15] clarified several clinical features of AIH patients differing between Japanese patients and patients of western countries. Additionally, the newest survey [16] revealed changing clinical features of Japanese AIH patients in the recent decades.

Despite the fact that female patients are still predominant (as shown in Table 1), the ratio of male patients was

shown to have gradually increased over time (female-to-male ratio: 12.0-fold [13], 9.5-fold [14], and 7.0-fold [15]). In addition, the rate of ANA-positive patients, which was reported to be 95.3% in a previous study [15], decreased to 89.1% (886 of 994 patients), and a reduced rate of ANA positivity was also mentioned as another notable finding [16]. However, at the same time, 43.6% of the ANA-negative patients were positive for ASMA (47 of 108 patients). Therefore, a total of 93.8% (932/994) were positive for either ANA or ASMA, and under the current Japanese guidelines, positivity for “either ANA or ASMA” is mentioned as a diagnostic criterion. Additionally, this report showed that the serum IgG level of patients was lower than in previous surveys. In a paper published in the 1990s, Japanese AIH patients showed markedly high serum IgG levels ($3,242 \pm 1,039$ mg/dL) [15]. Accordingly, the former Japanese criteria for diagnosing AIH (proposed in 1996) set “serum γ -globulin or IgG level $\geq 2,000$ mg/dL” as the cutoff value [59]; however, in the latest nationwide survey [16], the serum IgG levels of AIH patients at onset were decreased ($2,399 \pm 1,015$ mg/dL), and 38.9% of patients (392/1,056) showed serum IgG levels below 2,000 mg/dL. Given these varying clinical features, new guidelines of AIH for Japanese patients were published in 2013.

Guidelines for Managing Japanese AIH Patients

The diagnostic criteria of Japanese guideline are shown in Table 2. In response to the decreased IgG values of patients, the criterion of an increased IgG level was changed from “2,000 mg/dL” to “1.1 times the upper limit of normal” [60, 62]. In addition, unlike the former criteria, response to treatment has come to be included as a criterion for a diagnosis. One unique point in this guideline is that AIH can be diagnosed without histological findings, thereby allowing for the diagnosis of patients who cannot undergo a liver biopsy due to clinical issues, including elderly age, the presence of ascites and a bleeding tendency. However, since immunosuppressive therapies are sometimes accompanied by severe adverse events, physicians should make their best effort to obtain evidence supporting a diagnosis, and a histological assessment is recommended in as many cases as possible.

Of course, a complete AIH diagnosis cannot be obtained, even using these Japanese-specific diagnostic criteria, and the current Japanese guidelines therefore reference the 2 IAIHG scoring systems and their characteristics. The revised international diagnostic criteria have high sensitivity and are unlikely to miss atypical cases, such as those with a negative autoantibody test and/or elevated IgG levels. The simplified criteria have excellent

Table 2. Diagnosis and severity of AIH in the Japanese guideline 2013

<i>Diagnosis</i>
1. Exclusion of other, known, specific causes of liver injury
2. Presence of serum ANA or ASMA
3. High serum immunoglobulin G levels (>1.1 times the upper limit of normal)
4. Histological features such as interface hepatitis and/or plasma cell infiltration into the portal area
5. Excellent response to corticosteroid treatment
A typical case should fulfill criterion 1 and at least 3 of the remaining criteria
An atypical case of AIH should fulfill criterion 1 and 1 or 2 of the remaining criteria
<i>Severity</i>
<i>Clinical signs</i>
(1) Hepatic encephalopathy
(2) Reduction or disappearance of hepatic dullness
<i>Clinical laboratory tests</i>
(1) AST, ALT >200 IU/L
(2) Bilirubin >5 mg/dL
(3) Prothrombin time <60%
<i>Imaging tests</i>
(1) Hepatic atrophy
(2) Heterogeneous liver parenchyma pattern
Severe: should fulfill at least 1 of these 3 findings:
1. Clinical signs: (1) or (2) 2. Clinical laboratory tests: both (1) and (3), or both (2) and (3) 3. Imaging tests: (1) or (2)
Moderate: should fulfill these findings:
Clinical laboratory tests: 1 of the criteria [(1), (2), or (3)] or both (1) and (2), without clinical signs [neither (1) nor (2)], and imaging tests [neither (1) nor (2)]
Mild: none of the above criteria are observed
Adapted from the reference paper by Onji et al. [60].

diagnostic specificity and are helpful for identifying definitive cases of AIH and providing appropriate steroidal medication [60, 62]. Currently in Japan, AIH is diagnosed with comprehensive consideration of these 3 diagnostic criteria sets (the original Japanese diagnostic criteria and 2 IAIHG criteria sets).

Uniquely, the current Japanese AIH guidelines define the severity of AIH (Table 3). Patient conditions are recommended to be immediately evaluated according to the grading scale after the diagnosis, and severe-grade patients should be referred to a hepatologist due to the high risk of an unfavorable outcome. In addition, patients with intense jaundice or a prothrombin time of less than 60% should also be referred to a hepatologist, even for cases classified as moderate grade.

Table 3. Treatment for AIH in the Japanese guideline 2013

<i>Treatment</i>
1. Diagnostic confirmation, in principle, should be followed by corticosteroid treatment
2. Prednisolone should be administered at an initial daily dose of 0.6 mg/kg or more, and tapered according to improvements in serum aminotransferase and immunoglobulin G levels. The maintenance dose should be determined after achieving normalized aminotransferase levels
3. Ursodeoxycholic acid (600 mg/day) may be administered concomitantly during the tapering of the prednisolone dose, or alone in mild cases
4. Azathioprine (50–100 mg/day) should be administered to patients experiencing repeated relapses or those unable to tolerate the side effects of prednisolone
Adapted from the reference paper by Onji et al. [60].

Regarding treatment for AIH, based on the high responsiveness of Japanese patients to corticosteroids, steroidal monotherapy has been described as the initiation therapy. One unique point in the Japanese guidelines is that not only azathioprine but also ursodeoxycholic acid (UDCA) is mentioned as an optional treatment (Table 3). Despite the limited number of clinical studies, UDCA has been suggested to show clinical effectiveness in some Japanese patients [63] and may be prescribed alone in mild cases. In addition, UDCA can be considered for concomitant administration during the tapering of the prednisolone dose. However, UDCA monotherapy is not recommended to be administered in patients with a severe disease status.

Conclusions

We herein addressed the clinical features of AIH patients in eastern countries around Japan (East Asia, Southeast Asia, and South Asia). The disease prevalence is considered to be lower than in western countries. A few young patients with type 2 AIH may be found in South Asian countries; however, in East Asia and Southeast Asia, most patients are middle-aged women with type 1 AIH who respond well to steroid-based immunosuppressive therapy. Regarding the genetic characteristics, HLA-DR4 is suggested to be associated with the development of AIH in Asian patients, particularly in East Asia. In addition, AIH may be triggered by some culture- or tradition-related remedies, such as herbal medicines. The

IAIHG scoring systems are commonly used as standard diagnostic tools for AIH in Asian countries. Consecutive national surveys in Japan have suggested changes in the clinical features of AIH patients in East Asia. Based on these results, original guidelines for Japanese patients were proposed in 2013 with some population-specific unique proposals for diagnosis and treatment.

Disclosure Statement

The authors declare no conflicts of interest regarding this work.

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