Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver*

Introduction

Autoimmune hepatitis (AIH) was the first liver disease for which an effective therapeutic intervention, corticosteroid treatment, was convincingly demonstrated in controlled clinical trials. However, 50 years later AIH still remains a major diagnostic and therapeutic challenge. There are two major reasons for this apparent contradiction: Firstly, AIH is a relatively rare disease. Secondly, AIH is a very heterogeneous disease.

Like other rare diseases, clinical studies are hampered by the limited number of patients that can be included in trials. Possibly and more importantly, the interest of the pharmaceutical industry to develop effective specific therapies for rare diseases is limited due to the very restricted market for such products. The wide heterogeneity of affected patients and clinical manifestations of the disease limits both diagnostic and further therapeutic studies. AIH's age spectrum is extremely wide, it can affect small infants and can manifest for the first time in octogenarians. AIH can run a very mild subclinical course or be very acute, rarely leading to fulminant hepatic failure. AIH sometimes demonstrates quite dramatic disease fluctuations with periods of apparent spontaneous remissions, acute flares and/or smouldering disease. AIH can be associated with a number of other hepatic conditions, in particular the cholestatic liver diseases; primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), but also with drug-induced liver injury (DILI), alcoholic or non-alcoholic steatohepatitis (NASH) or viral hepatitis. Each condition provides special diagnostic and therapeutic challenges. Despite these challenges and complexities, diagnosis and treatment of AIH has seen striking progress, and now patients in specialised centres have an excellent prognosis, both in respect to survival and to quality of life.

The aim of the present Clinical Practice Guideline (CPG) is to provide guidance to hepatologists and general physicians in the diagnosis and treatment of AIH in order to improve care for affected patients. In view of the limited data from large controlled studies and trials, many recommendations are based on expert consensus. This is to some extent a limitation of this EASL-CPG, but at the same time it is its special strength: consensus in this guideline is based on intensive discussions of experts from large treatment centres. The core consensus group has experience of over one thousand AIH patients managed personally, and the recommendations have been reviewed by both the EASL Governing Board as well as external experts, who have a similarly wide personal experience. Therefore, the guidelines are a resource of information and recommendations based on the largest experience available thus far. At the same time, we formulate key scientific questions that result from the consensus discussions on the limitations of our knowledge. All recommendations of this CPG were agreed upon unanimously (100%) consensus. Grading of the recommendations is based on the GRADE system for evidence (Table 1) [1].

Epidemiology of AIH

AIH is an non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression [2–5]. The disease, if untreated, often leads to cirrhosis, liver failure and death.

AIH is considered relatively rare, as its prevalence ranges from 16 to 18 cases per 100,000 inhabitants in Europe [6–11]. Until recently, the incidence and prevalence of AIH on a population-based level was assessed in only two studies [6,9]. Interestingly however, higher prevalence rates have been reported in areas with quite stable populations. For instance, prevalence rates of 42.9 cases per 100,000 and 24.5 cases per 100,000 inhabitants have been reported in Alaska natives [12] and New Zealand [9], respectively. In addition, a large Danish nationwide population-based study assessed the incidence and prevalence of AIH in Denmark during a nearly 20 year time period ranging from 1994 to 2012 including 1721 AIH patients [13]. The most striking observation in that study was the marked increase in AIH incidence over time, which could not be attributed to a relative

Received 30 June 2015; accepted 30 June 2015
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Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ANCA, Antineutrophil cytoplasmic antibodies; APECED, Autoimmune polyendocrinopathy-cadidiasis ectodermal dystrophy; AS, acute severe autoimmune; CNI, Calcineurin inhibitor; CPG, Clinical Practice Guideline; DEXA, Dual energy x-ray absorptiometry; DILI, Drug-induced liver injury; HAI, Hepatitis activity index; HBV, Hepatitis B virus; HLA, Human leukocyte antigens; HRQoL, Health related quality of life; IBD, Inflammatory bowel disease; IgG, Immunoglobulin G; LBR, Live birth rate; LT, Liver transplantation; MMF, Mycophenolate mofetil; MRCP, Magnetic resonance cholangiopancreatography; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; PBC, Primary biliary cirrhosis; PROM, Patient reported Outcome Measures; PSC, Primary sclerosing cholangitis; SCBU, Special care baby unit; SMA, Smooth muscle antibodies; TPMT, Thiopurine methyltransferase.

Table 1. Grading of recommendations.

I	Randomised controlled trials
II-1	Controlled trials without randomisation
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Adapted from: [1].

change in case ascertainment rates. Actually, the incidence rate of AIH in Denmark has nearly doubled between 1994 to 2012, reaching a point prevalence in 2012 of 24/100,000 (35/100,000 for females) [13].

AIH prevalence and clinical expression seem to vary according to ethnicity. Alaskan natives appear to have a high frequency of acute icteric disease at the disease onset [12], and the disease is more common and more severe in North American Aboriginal/First Nations populations compared with predominantly Caucasian, non-First Nations populations [14]. African-American patients more commonly have cirrhosis, a higher frequency of treatment failure and higher mortality than white American patients [15,16]. Mexican Mestizos commonly show cirrhosis at initial evaluation [17] and patients of Hispanic origin are characterized by an aggressive presentation both biochemically and histologically with a very high prevalence of cirrhosis and cholestatic features [18,19], whereas patients of Asian or other non-European Caucasoid background have very poor outcomes [18,20]. Although most of the above mentioned studies are retrospective and have been performed in tertiary centres, these observations have led to the assumption that AIH has diverse clinical phenotypes and outcomes in different ethnic groups within a country and between countries. These differences may reflect genetic predispositions, indigenous etiological agents, and/or pharmacogenomic mechanisms, but they might also be primarily due to complex socioeconomic reasons such as variations in the delivery of health care, delayed diagnosis as well as competing risk factors [21].

1. Prevalence of AIH ranges from 15 to 25 cases per 100,000 inhabitants in Europe and is increasing in both women and men **(II-2)**
AIH can affect all populations and all age groups **(II-2)**

Clinical spectrum

Clinical features of AIH

In the early 1950s, a novel type of chronic hepatitis with several particular features, such as a predilection for young women, a progressive and usually fatal outcome accompanied by arthralgia, endocrine dysfunction, cutaneous striae and acne, and very high levels of immunoglobulins in the serum that correlated with an excess of plasma cells in the liver, was reported firstly by the Swedish physician Jan Waldenström [22] and later by Kunkel *et al.* [23]. In 1955, the lupus erythematosus cell phenomenon was demonstrated in these patients and therefore, the term "lupoid hepatitis" was introduced by the group of Ian Mackay in 1956 [24], but ten years later this term was replaced by 'Autoimmune hepatitis' [25], which after a variety of different terms was accepted in the 1990s by the International AIH Group (IAIHG) as the final one [26].

It is now well established that AIH is a clinically distinct syndrome characterized by a large heterogeneity of clinical, laboratory and histological manifestations (Table 2). Therefore, AIH should be considered in any patient with acute or chronic liver disease, particularly if hypergammaglobulinemia is present, and if the patient has features of other autoimmune diseases (Table 3) [2–4,26–28]. The disease can also affect males (ca. 25–30% of all AIH patients) and may present at any age and in all ethnic groups [8–13,29–33]. In most studies, a bimodal age pattern at presentation has been reported with one peak during childhood/teenage years and another in middle age between the 4th and 6th decade of life [8,11,13,33,34]. Recent studies have shown that an increasing number of patients are diagnosed also at older ages (above 65 years) [30–32,35]. Recently it has been shown that appropriate attention should also be paid to the health related quality of life (HRQoL) parameters, since a high rate of previously unrecognised mental impairment with depression and anxiety symptoms are present in patients with AIH [36].

The spectrum of clinical manifestations is variable, ranging from no obvious signs or symptoms of liver disease to a severe and almost identical form of an acute or even fulminant episode of viral hepatitis (Table 2) [3,4,37]. Indeed, approximately 25% of patients present with an acute onset of AIH, which is phenotypically similar to acute hepatitis cases of other causes [33,38]. However, acute presentation of AIH actually may contain two different clinical entities. One is the acute exacerbation of chronic AIH (acute exacerbation form of undiagnosed or misdiagnosed AIH cases) and the other is the genuine acute AIH without chronic histological changes (acute form of AIH; Table 2) [33,37–39]. Of note, in some patients with acute presentation of AIH, immunoglobulin G (IgG) levels may be within the normal range and antinuclear (ANA) and/or smooth muscle antibodies (SMA) as first screening may be negative and thus, the clinician may not consider AIH [3,4,34,40,41]. A more extensive and sensitive autoimmune liver serology testing could be helpful in such cases. Furthermore, in some patients autoantibodies may only become positive some months later in the disease course. Some of these acute cases of AIH may rarely progress to acute liver failure and this should be kept in mind. The identification of AIH as the aetiology of acute hepatitis and/or fulminant hepatic failure is very important because a delay of the diagnosis and thus delay of initiation of therapy results in poorer prognosis of AIH, whereas administration of immunosuppression with steroids might avoid the need for liver transplantation (LT) [33,37–39,41–43].

Commonly (about one third of patients), the clinical presentation is characterized by the presence of one or more of several non-specific symptoms listed in Table 2 [8,11,13,18,21,29,33,44,45]. Amenorrhea is also common whereas maculopapular skin rash and unexplained low-grade fever are rare features. Physical findings may be normal, but sometimes hepatomegaly, occasionally painful, splenomegaly and, when frank cirrhosis has developed, signs and symptoms of chronic liver disease like palmar erythema and spider naevi may be found. In advanced stages, the clinical picture of portal hypertension dominates including