Auto immune hepatitis

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Abstract

To provide an update of the latest trends in epidemiology, clinical course, diagnostics, complications and treatment of auto immune hepatitis (AIH). A search of the MEDLINE database was performed using the search terms: “auto immune hepatitis”, “clinical presentation”, “symptoms”, “signs”, “diagnosis”, “auto antibodies”, “laboratory values”, “serology”, “histopathology”, “histology”, “genetics”, “HLA genes”, “non-HLA genes”, “environment”, “epidemiology”, “prevalence”, “incidence”, “demographics”, “complications”, “HCC”, “PBC”, “PSC”, “corticosteroid”, “therapy”, “treatment”, “alternative treatment”. English-language full-text articles and abstracts were considered. Articles included reviews, meta-analysis, prospective retrospective studies. No publication date restrictions were applied. AIH is an immune mediated progressive inflammatory liver disease that predominantly affects middle-aged females but may affect people of all ages. The clinical spectrum of AIH is wide, ranging from absent or mild symptoms to fulminant hepatic failure. The aetiology of AIH is still unknown, but is believed to occur as the consequence of an aberrant immune response towards an un-known trigger in a genetically susceptible host. In the absence of a gold standard, diagnosis is based on the combination of clinical, biochemical and histopathological criteria. Immunosuppressive treatment has been the cornerstone of treatment since the earliest description of the disease in 1950 by Waldenström. Such treatment is often successful at inducing remission and generally leads to normal life expectancy. Nevertheless, there remain significant areas of unmet aetiological a clinical needs including fundamental insight in disease pathogenesis, optimal therapy, duration of treatment and treatment alternatives in those patients unresponsive to standard treatment regimens.

Key words: Auto immune hepatitis; Diagnosis; Liver; Epidemiology; Treatment

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Core tip: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder of unknown aetiology, which can lead to hepatic failure and premature
death when untreated. In AIH there is no existence of a pathognomonic feature and therefore the diagnosis rests on a combination of immunological, biochemical, and histological features together with exclusion of other liver diseases. Due to large heterogeneity of the disease, AIH might be unrecognised. Immunosuppressive treatment has been the cornerstone of treatment. Such treatment is often successful at inducing remission. For most patients life long treatment is indicated. In patients in whom all treatments fail, liver transplantation remains a final option.

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INTRODUCTION
The first to describe a chronic form of hepatitis in young women was Jan Waldenström in 1950[1]. Later, the disease was associated with other autoimmune diseases and was termed “lupoid hepatitis” because of the presence of antinuclear antibodies and lupus erythematosus cells[2]. These observations led to the idea that the foundation of this disease was a loss of immunological tolerance. The term Auto Immune Hepatitis (AIH) in its current meaning was introduced by Mackay and colleagues in 1965 when the concept of autoimmunity was acknowledged at an international meeting[3].

AIH is now recognized as a relatively rare chronic inflammatory liver disease predominantly affecting females in which a loss of tolerance against hepatic tissue is assumed. Based on the type of serum autoantibodies, AIH can be subdivided into two types: type 1 AIH, identifiable by antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA), and type 2 AIH, predominantly found in children and defined by antibodies against liver kidney microsomes type 1 (anti-LKM-1) or for anti-liver cytosol type 1 antibodies[4,5].

EPIDEMIOLOGY
There are few studies that have investigated the epidemiology of AIH. The majority of these studies are hampered by the fact that no predefined criteria for disease diagnosis were applied. In some older studies there has been admixture of patients with chronic hepatitis C and finally some of the studies may have been subject to tertiary referral bias (Table 1).

Nevertheless, incidence data are more or less comparable in Western Europe, ranging from 0.8 to 3 per 100000 with a prevalence ranging from 11 to 24 per 100000[6-9]. In Asia AIH seems to be less frequent, with incidence numbers ranging between 0.08 and 0.15 in Japan[10].

Substantially higher prevalence data of 42.9 cases per 100000 were found in a well defined native Alaskan population, although it should be noted that this study involved a small catchment area and a very limited number of patients[11]. Based on the available studies it is estimated that 11%-20% of all cases of chronic hepatitis in Western countries is caused by AIH[12]. The prevalence of AIH is still gradually increasing. Whether or not this reflects a true rise in incidence, as seen in other immune-mediated diseases like Crohn’s disease, increased awareness of the disease or different diagnostic criteria is unknown.

Women are affected more frequently than men with a sex ratio of around 4:1[9]. In women a bimodal age pattern is usually seen, one in the late teens and one around the menopause but it should be stressed that disease can develop in all age groups and both genders[4,13].

PATHOGENESIS
The etiology of AIH remains unknown and fundamental questions regarding disease pathogenesis remain to be resolved. It is generally believed that AIH occurs in a genetically susceptible host as the consequence of an exaggerated immune reaction towards hepatic tissue[14]. Such a response can occur when effector lymphocyte responses are abundant and inappropriate leading to tissue damage, or, alternatively, when there is a numerical and/or functional defect in regulatory T cells (Treg) controlling such responses. This defect is more obvious at disease presentation than during treatment induced remission, where a partial recovery is observed.

Whilst abundant pro-inflammatory responses have been identified in most, if not all immune-mediated diseases, it has been very difficult to gain evidence for a primary defect in regulatory T cells in the majority of these diseases. Tregs isolated from children and adults with AIH were profoundly dysfunctional, suggesting that an underlying Treg deficiency plays a permissive role in the pathogenesis of AIH[15-17].

More recent studies omitted to find either functional or numerical Treg impairments in AIH patients and thus the question as to whether AIH is the result of defective immunoregulation warrants further investigation.

A third, not mutually exclusive mechanism may relate to molecular mimicry, which has been proposed as a mechanism by which exogenous substances may trigger an immune response against autoantigens. Such a response may spark an inflammatory reaction and the resulting hepatocellular injury may give rise to the release of other previously hidden antigens that may further fuel the inflammatory reaction. Exogenous pathogens implicated in this process include,
amongst others, the hepatitis C virus. A sequence homology between HCV polyprotein and cytochrome P4502D6 (CYP2D6) was previously reported, which was identified as anti-LKM-1 autoantibodies. Indeed, anti-LKM-1 is seropositive in up to 10% of HCV patients. Other proposed triggers include other hepatotropic viruses, as well as drug induced liver injury caused by antibiotics (including nitroufurantoin and minocycline), statins and anti-TNF agents.

### GENETIC FACTORS

Genetic factors have long been implicated in disease pathogenesis yet systematic studies addressing the genetic epidemiology of AIH including familial occurrence, disease concordance in twins or ethnic differences in disease prevalence are lacking. Nevertheless, there are several observations that support a genetic basis for AIH. These include the association with other autoimmune diseases with a known genetic basis in up to a quarter of patients. Additionally, associations with alleles of the Major Histocompatibility Complex (MHC) that encode the Human Leucocyte Antigens (HLA) were already described in the late seventies and confirmed and refined thereafter in numerous studies in different ethnic groups.

Such associations are found with most autoimmune diseases, most likely because they contribute to the specificity of immune reactions. HLA typing of patients with AIH reveals strong association with the HLA-DRB1 locus, with the haplotypes DRB1*0301 (HLA-DR3) and DRB1*0401 (HLA-DR4) as the main susceptibility factor in white Northern Europeans and North Americans. Intriguingly there is evidence for substantial genetic heterogeneity in AIH with different MHC associations in different ethnic populations. Thus, in Japanese patients HLA-DRB1*0405 is the most important susceptibility allele whereas primary associations with DRB1*0404 were found in Mexican patients.

The HLA alleles not only determine overall disease susceptibility but appear also to act as modifiers of the clinical phenotype. For instance, HLA-DR4 was found to be associated with female gender, less severe disease, more common autoimmune disease, and older age of onset. Despite the fact that the MHC loci confer a 6 to 7 fold increased disease risk, these variants alone cannot explain the genetic predisposition for AIH. Genes outside the MHC have only been studied in candidate gene approaches involving limited numbers, making them prone to overestimation of significance. Most extensively studied is the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene. A recent study in the Netherlands involving a substantial number of patients however observed no significant differences in allele and genotype frequencies of the CTLA-4 gene between AIH patients and controls.

More recently, genome-wide association studies have emerged as a powerful and unbiased approach for the identification of new genetic susceptibility loci in autoimmune diseases. Very recently this methodology was applied in a multicentre cohort of type 1 AIH patients. This study confirmed the involvement of the MHC region and identified SH2B3 as the first genetic risk factor outside the MHC region. In addition, several other loci were identified supporting the thesis that AIH has a complex genetic basis.

### CLINICAL FEATURES

The clinical manifestation of AIH can range from mild or severe symptoms to fulminant hepatic failure. In all patients with liver disease AIH should be considered, so that that appropriate treatment can be instituted without delay. Up to 40 percent of patients presents with acute hepatitis, characterizes by right upper-quadrant abdominal pain, fatigue, jaundice and arthralgia. However a fulminant manifestation or a long sub clinical course with only minimal increase of liver enzymes and non specific symptoms, such as arthralgia or fatigue, may be seen.

Clinical manifestations of AIH may vary among ethnic groups. Thus, non-Caucasian patients (the majority being from African-American descent) had more aggressive disease at initial presentation, lower reaction to immunosuppressive therapy, and worse outcomes when compared to Caucasian patients. Higher rates of cirrhosis were found in Hispanic vs Caucasian patients, and a trend towards worse survival among Asians.

Other autoimmune diseases are common in up to

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**Table 1 Studies of incidence and prevalence of autoimmune hepatitis**

| Ref.     | Year | Cases | Incidence/100000 | Prevalence/100000 |
|----------|------|-------|------------------|-------------------|
| Toda et al[26] | 1997 | 496   | 0.8              | -                 |
| Whalley et al[23] | 2007 | 200   | 3.0              | -                 |
| Werner et al[8] | 2008 | 473   | 0.85             | 10.7              |
| Grenbæk et al[5] | 2014 | 1721  | 1.68             | 23.9              |
| Gerven et al[6] | 2014 | 1313  | 1.1              | 18.3              |
| Ngu et al[39] | 2010 | 138   | 2.8              | 24.5              |
| Delgado et al[40] | 2013 | 100   | 0.67             | 11.0              |
| Primo et al[39] | 2004 | 13    | 1.37             | 11.61             |
| Hurﬁlbert et al[39] | 2002 | 77    | -                | 42.9              |
40% of AIH patients. They included, among others thyroid disease, diabetes, inflammatory bowel disease and rheumatoid arthritis. A recent study demonstrates that celiac disease is more prevalent among AIH patients compared to the general population\(^9\). In addition, AIH may have cholestatic features that can resemble primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) and overlap with these diseases have been described in 10%-20% and 2%-8% of cases, respectively\(^{9,14,52-55}\) (Table 2). So far, there have not been uniform definitions or diagnostic criteria for the overlap of AIH with PBC or PSC. It is still under debate as to whether these overlap syndromes represent variants of the main autoimmune liver diseases or hallmarks of a separate entity\(^{56}\). The presence of features of different diseases can occur simultaneously as well as sequentially in each form of overlap syndromes. AIH and PBC are the most frequently described autoimmune liver diseases. The pattern of abnormalities in laboratory tests can help determine the origin of the disease. In AIH a hepatic pattern is found, and a primarily cholestatic pattern in PBC; in addition, elevation of IgG is characteristic of AIH, an increase in IgM is commonly found in PBC patients.

Due to an absence of a well validated scoring system for the diagnosis of PBC-AIH overlap, the criteria developed by Chazouillères \(\text{et al}\)\(^{57}\) are commonly applied.

In various reports AIH-PSC overlap syndrome has been described and is characterised by ANA and/or SMA seropositivity, hypergammaglobulinaemia and interface hepatitis - all features typical of “classical” AIH - in conjunction with cholestatic biochemical changes, frequently associated with inflammatory bowel disease, and histological evolution to fibrous obliterator cholangitis, ductopenia, portal tract oedema and/or bile stasis\(^{58}\).

| Table 2 Presentation and symptoms in autoimmune hepatitis |
|----------------------------------------------------------|
| **Acute hepatitis**                                      |
| **Chronic hepatitis**                                    |
| **Hepatomegaly**                                         |
| **Splenomegaly**                                         |
| **Spider naevi**                                         |
| **Palmar erythema**                                      |
| **Non-specific symptoms:**                               |
| **Tiredness**                                            |
| **Fever**                                                |
| **Loss of appetite**                                     |
| **Upper abdominal pain**                                 |
| **Arthralgia**                                           |

**Extr-hepatic autoimmune disease (most common mentioned):**

- Thyroiditis: 10%-23%
- Primary biliary cirrhosis: 10%-20%
- Diabetes: 7%-9%
- Primary sclerosing cholangitis: 2%-8%
- Rheumatoid arthritis: 2%-5%
- Celiac disease: 1%-2%

**Laboratory abnormalities**

AIH is suggested by a patient with elevated Alanine-aminotransferase (ALT) and Aspartate transaminase (AST) activity, raised Immunoglobulin G (IgG), high titres of circulating antibodies, negative serum tests and exclusion of toxic hepatitis. However not all these laboratory findings need to be present in an individual patient.

Elevation of serum IgG is a common finding in AIH\(^{60}\), but normal IgG levels may be found in up to 30% of patients\(^{55,62}\).

Auto antibodies are the hallmark of AIH and can constitute an important part of the diagnostic work up. The classic antibodies associated with AIH are Antinuclear antibodies (ANA), anti-smooth-muscle antibodies (ASMA) and Anti Liver kidney microsomal (LKM-1). About 70%-80% of AIH patients have significant titres \(\geq 1:40\) of ANA or ASMA and overall 3%-4% have anti LKM-1, while up to 20% are seronegative for these antibodies\(^{60}\).

ANA are the most commonly found auto antibodies in AIH, yet are rather non-specific since they can be found in a large variety of diseases as well as in healthy individuals\(^{63}\). ANA may be the only antibody present or may occur in conjunction with ASMA. ASMA are the second major class of antibodies which have proved useful in the diagnosis of AIH. Although less prevalent than ANA they are more specific\(^{64}\).

Autoantibody detection not only supports in the diagnosis but also classifies between type 1 and type 2 AIH. Type 1 AIH is associated with the presence of ANA and/or SMA and type 2 with the presence of anti-LKM-1 and/or anti-liver cytosolic-1 (LC-1). In Northern Europe and North America type 2 AIH accounts for less than 10% of all patients\(^{65}\).

Antibodies to soluble liver antigen (SLA) or liver pancreas antigen (LP) are found in 10%-30% of patients with AIH. These antibodies are specific for AIH and may prove useful in the diagnosis\(^{65}\). Antibodies to actin and atypical peripheral anti-neutrophilic cytoplasm are also commonly seen in type 1 AIH, however their applicability is limited due to lack in specificity\(^{59}\).

**Liver histology**

A liver biopsy is usually necessary to confirm the diagnosis, provide histological assessment of disease severity and exclude other causes of hepatitis. There are no individual histological criteria that prove the diagnosis of AIH\(^{66}\). Interface hepatitis (or piecemeal necrose) is the histological hallmark of AIH and is a process of inflammatory infiltration and erosion of the hepatic parenchyma at the junction of the portal
Table 3  Simplified diagnostic criteria for auto immune hepatitis

| Variable                                    | Cutoff                | Points |
|---------------------------------------------|-----------------------|--------|
| ANA or ASMA                                  | ≥ 1:40                | 1      |
| ANA or ASMA, or LKM-1, or SLA                | ≥ 1:80                | 2      |
| IgG                                         | Positive              |        |
| Liver histology (evidence of hepatitis is a necessary condition) | > Upper normal limit | 1      |
|                                             | > 1.10 times upper normal limit | 2      |
|                                             | Compatible with AIH   | 1      |
|                                             | Typical AIH           | 2      |
|                                             | Yes                   | 2      |
|                                             | ≥ 6: probable AIH     |        |
|                                             | ≥ 7: definite AIH     |        |

ANA: Antinuclear antibodies; ASMA: Anti-smooth-muscle antibodies; LKM-1: Anti Liver kidney microsomal; IgG: Immunoglobulin G.

tract. It is found in 84%-98% of patients, but can also be seen in patients with drug-induced and viral hepatitis. The infiltrates consist of hepatic mesenchymal cells containing lymphocytes, plasma cells and histiocytes that typically accompany these cells. Patients presenting with chronic AIH typically have plasma cells infiltrated at the interface and throughout the lobule. Plasma cells are not invariably present and paucity of plasma cells does not therefore exclude a diagnosis of AIH. They may be absent in up to one third of the patients. In a recent study, emperipolesis and rosette formation appear superior histological predictors of AIH when compared to the typical histological features of interface hepatitis and plasma cells.

Diagnosis scoring system

Because there is no golden standard for the diagnosis of AIH, diagnostic scoring systems have been established that support the diagnosis in most of patients. The IAIHG scoring system, originally published in 1993 and revised in 1999, was developed as a search tool to ensure comparability of study populations. Despite a high degree of sensitivity (100%) and specificity (90%), these criteria have been proven impractical in the day to day clinical practice.

In 2008 the IAIHG produced a simplified system for the diagnosis of AIH which is less complex and enhances applicability in clinical practice. This system is based on four variables: presence and level of anti bodies, IgG concentration, typical histological features and absence of viral markers (Table 3). Recently three studies report that the simplified scoring system performs with high specificity (97%-99%) and lower sensitivity (81%-88%) when compared to the original diagnostic criteria yet requires further prospective validation.

TREATMENT

Indication of treatment

The short and long term efficacious of immune suppression in patients with AIH has been described unequivocally. When left untreated, an estimated 40% of patients will die within six months of diagnosis. When treated adequately, the 20-year survival rate for all treated patients exceeds 80%, and life expectancy is similar to that of age and sex matched normal subjects from the same geographical area.

Updated treatment guidelines have recently been emerged by the European Association for the Study of the Liver (EASL) in 2015, the British Society of Gastroenterology in 2011 and the American Association for the Study of Liver Diseases (AASLD) in 2010. Patients with AST levels 10-fold the upper normal limit, or fivefold the upper normal limit in concurrence with IgG levels at least twice the upper normal limit, or histological features of bridging necrosis or multinodular necrosis, should be offered immunosuppressive treatment because of clear survival benefit. Patients not satisfying these criteria must be personalized and treatment should be based on clinical judgement.

Standard treatment

Current therapeutic strategies for AIH consist of an induction with prednisone and frequently include subsequent addition of azathioprine (AZA) as steroid-sparing maintenance therapy. Prednisone is introduced at a dose of 1 mg/kg with a maximum of 60 mg/d in monotherapy or a maximum of 30 mg/d in combination treatment. After AST and ALT normalize, prednisone alone can be reduced by 10 mg/wk until a dose of 20 mg.

Patients treated with combination therapy can reduce prednisone by 5 mg/wk until 15 mg. A slower reduction is advised after this point. For maintenance treatment AZA can be used at a dose 1-2 mg/kg per day either alone or in combination with low dose prednisone. A recent review based on available randomised controlled trials found that prednisone monotherapy and prednisone in combination with AZA are both feasible induction therapies for AIH, while maintenance therapy prednisone and AZA and Monotherapy AZA are superior to prednisone monotherapy. AIH patients...
treated with corticosteroids and/or AZA have the risk of many side effects on both drugs. The side effects of long term treatment with corticosteroids are well known; acne, moon shape face, striae, weight gain and loss of bone density. Adverse effects of thiopurines are common and generally occur shortly after the start of therapy. They include allergic reactions, flu-like illness, nausea fever, malaise, rash, abdominal pain, hepatotoxicity, pancreatitis and myelosuppression[83,85-87]. The principal side effects of AZA are cytopenia and liver test abnormalities, which may be difficult to distinguish from inherent AIH disease activity.

**Remission and relapse**
Remission of previously symptomatic patients is defined as a complete normalisation of all inflammatory parameters, including AST, ALT, bilirubine, IgGs, recovery from symptoms and inactive liver histology[4,8,92]. In 80%–90% of patients with moderate/severe AIH, serum ALT decreases after starting treatment. Usually a decrease is seen within two weeks. As transaminase decrease, clinical symptoms resolve and liver functions shows marked improvement within 3-6 mo after starting prednisone treatment either with or without AZA[88].

There is no prescribed duration of the length of treatment. Because histological restore lags behind clinical and biochemical improvement by 3-8 mo, treatment should be continued for at least this period[86,89]. Proper patient selection including sustained remission on immunosuppressive Monotherapy for a minimum of 2 years can markedly improve the success rate of treatment withdrawal[90]. The AASLD and EASL guidelines recommend treatment withdrawal, when serum liver and immunoglobulin levels have been repeatedly normal for a period of at least two years. Liver biopsy prior to termination of treatment is preferred[4,80]. Relapse is characterized by an increase in ALT levels (three times upper normal limit) and/or increase of serum IgG level to more than 2 g/L following tapering of steroid doses or after complete withdrawal of immunosuppression[41]. Literature from the 1970s showed a high risk of relapse after drug withdrawal[88,91], but this was later disputed and it was recommended that drugs withdrawal should be attempted[92]. A more recent retrospective analysis found that relapse occurred in almost all patients with AIH when immunosuppressive medication was discontinued or tapered[4,92,93]. Relapse occurred despite prior attainment of complete remission, including a histological inactive follow up biopsy prior to tapering in a subgroup of patients. In patients who have relapsed once, a subsequent attempt to withdrawal therapy was invariably associated with the re-occurrence of a relapse[95]. Since repeated relapses were associated with a poorer long term prognosis patients should receive life long treatment[94,95]. A lifelong follow up should occur in patients who successfully stopped immunosuppression, while a relapse can occur 10 years later[93].

**Alternative treatment**
In up to 10% of AIH patients, the therapeutic strategy of prednisone and AZA is unsuccessful, due to intolerable side effects or lack of clinical response[4,81]. In patients who fail on standard therapy, alternative immunosuppressive treatments have been tried with encouraging results. Cyclosporine[96-98], tacrolimus[99,100], methotrexate[101], cyclophosphamide[102] and mycophenolate mofetil[103-105] have been tried, with varying degrees of success, as a replacement for AZA.

In a small recent study allopurinol was added to the AZA or mercaptopurine treatment in patients who fail treatment due to ineffectiveness or intolerance, due to skewed thiopurine metabolism. The combination of low dose thiopurines and allopurinol proved an effective and well-tolerated alternative in the treatment of AIH. Larger and controlled studies are needed to confirm these outcomes[106]. As an alternative for prednisone, budesonide is receiving considerable attention.

In two recent studies in patients with noncirrhotic AIH oral budesonide, in combination with azathioprine, induces and maintains remission. This treatment causes fewer steroid-specific side effects[107,108]. Routine use is not currently recommended, while the trial duration is short and the fact that no follow up date were presented[81]. AZA is the prodrug of 6-mercaptopurin (6-MP) and is converted into 6-MP in a nonenzymatic manner before exhibiting its antiproliferative and immunosuppressive properties. In patients with ulcerative colitis and Crohn’s disease 6-MP has a beneficial role in AZA-intolerant patients[109]. In patients with AIH and AZA intolerance, 6-MP seems to be an effective and well-tolerated second line treatment[110]. The use of 6-thioguanine 6-TG), an agent more directly leading to down-stream active metabolites of AZA, showed clinical improvement in

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**Table 4** Indication for treatment of auto immune hepatitis (adapted from Manns et al[4])

| Absolute | Relative |
|----------|----------|
| Serum AST ≥ 10 fold ULN | Symptoms (fatigue, arthralgia, jaundice) |
| Serum AST ≥ 5 fold ULN and IgG level ≥ twice normal | Serum AST and/or IgG less than absolute criteria |
| Bridging necrosis or multicinar necrosis on histological examination | Interface hepatitis |

AST: Aspartate transaminase; ULN: Upper limit normal; IgG: Immunoglobulin G.
three AIH patients intolerant to AZA. A prospective evaluation of 6-TG as possible immunosuppressive drug in AIH patients is warranted[11].

COMPLICATIONS AND PROGNOSIS

Complications in AIH are comparable to those seen in other liver diseases and in rare cases AIH presents by the occurrence of hepatic encephalopathy[112,113]. Liver fibrosis is often present at diagnosis and a subgroup of patients have already cirrhosis at presentation[8,68] suggesting that the disease has gone unrecognized for a significant period prior to diagnosis. When left untreated, an estimated 40% of patients will die within 6 mo of diagnosis[89,91,114]. In some patients without proper treatment, AIH progresses to cirrhosis and eventually Hepatocellular carcinoma (HCC). The presence of cirrhosis at diagnosis or during treatment and the need for long-term immunosuppressive therapy have been observed as risk factors for malignant transformation[115]. In addition risk factors for HCC furthermore include male gender, advanced stage disease, portal hypertension as ascites and esophageal varices[116]. HCC occurs in 1%-9% of AIH patients[116-118], which is less frequently compared to patients with chronic viral hepatitis[119]. Imaging with ultrasonography or computed tomography should be conducted every 6-12 mo. In patients who develop liver failure, liver transplantation needs to be considered[46,120]. When AIH is indicated for transplantation, transplanted patients, practically compared to other chronic liver diseases, have an excellent 5 year survival of between 78%-91%[121-123]. The recurrence rate of AIH after initial successful transplantation is problematic and occurs in around 30% of patients[124].

CONCLUSION

AIH is a relatively rare disease of unknown aetiology. Many factors contribute to the diagnosis, which is characterized by a female predominance, historically evidence of portal hepatitis in the absence of viral markers, hypergammaglobulinemia, the presence of auto antibodies in serum, plasmacellular infiltrates and an optimal response to steroids in most patients. In AIH there is no existence of a pathognomonic feature and therefore the diagnosis rests on a combination of immunological, biochemical, and histological features together with exclusion of other liver diseases. Due to large heterogeneity of the disease, AIH might be unrecognised. The clinical manifestation of AIH can range from mild or severe symptoms to fulminant hepatic failure. AIH generally responds to immunosuppressive treatment and treatment is required as soon as the diagnosis is made. For most patients lifelong treatment is indicated. In patients in whom all treatment attempts fail liver transplantation needs to be considered.

AIH remains a major diagnostic and therapeutic challenge. Growing insights into the clinical presentation of AIH highlights the importance of evaluation of the current diagnostic criteria, role of genetic and environmental factors, as well as the development of new treatment strategies.

REFERENCES

1. Waldenström J. [Liver, blood proteins and nutritive protein]. Dtsch Z Verdau Stoßwechsel kr 1953; 9: 113-119 [PMID: 13150939]
2. Cowling DC, Mackay IR, Taft LL. Lupoid hepatitis. Lancet 1956; 271: 1235-1326 [PMID: 13386250]
3. Mackay IR, Weiden S, Hasker J. Autoimmune hepatitis. Ann N Y Acad Sci 1965; 124: 761-780 [PMID: 5214838 DOI: 10.1111/ j.1749-6632.1965.tb09000.x]
4. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 51: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]
5. Czaja AJ. Current and future treatments of autoimmune hepatitis. Expert Rev Gastroenterol Hepatol 2009; 3: 269-291 [PMID: 19485809 DOI: 10.1586/egh.09.18]
6. Bober KM. Prevalence and epidemiology of autoimmune hepatitis. Clin Liver Dis 2002; 6: 635-647 [PMID: 12362572 DOI: 10.1016/S1089-3261(02)00021-1]
7. Gronbaek L, Vilsstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatology 2014; 60: 612-617 [PMID: 24326217 DOI: 10.1016/j.jhep.2013.10.020]
8. van Gerven NM, Verber BJ, Witte BL, van Especum KJ, van Buuren HR, Majers I, Visscher AP, Verschueren EC, van Hoek B, Coenraad MJ, Beuers UH, de Man RA, Drenth JP, den Ouden JW, Verdonk RC, Koek GH, Brouwer JT, Guijselaar MM, Vrolijk CM, Mulder CJ, van Nieuwkerck BM, Bouma G. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol 2014; 49: 1245-1254 [PMID: 25123213 DOI: 10.3109/00365521.2014.946083]
9. Werner M, Pytzh H, Ohlsson B, Almer S, Björnsson E, Bergquist A, Wallerstedt S, Sandberg-Gertåsen H, H ulcerante R, Sangfeld P, Weiland O, Danielsson A. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008; 43: 1232-1240 [PMID: 18609163 DOI: 10.1080/00365520802130183]
10. Toda G, Zeniya M, Watanabe F, Imawai M, Nishikawa K, Matsuji M, Tsuji T, Omata M. Present status of autoimmune hepatitis in Japan--correlating the characteristics with international criteria in an area with a high rate of HCV infection. Japanese National Study Group of Autoimmune Hepatitis. J Hepatology 1997; 27: 1207-1212 [PMID: 9201605 DOI: 10.1016/S0168-8278(97)00453-9]
11. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trainwinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol 2002; 97: 2402-2407 [PMID: 12358264 DOI: 10.1111/1572-0241.2002.06019.x]
12. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002; 36: 479-497 [PMID: 12143059 DOI: 10.1053/jhep.2002.34944]
13. Al-Chalabi T, Boccatto S, Portmann BC, McFarlane IG, Henehan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. J Hepatol 2006; 45: 575-583 [PMID: 16899323 DOI: 10.1016/j.jhep.2006.04.007]
14. Teufel A, Weinnmann A, Kahaly GJ, Center C, Piendl A, Wörs M, Lohse AW, Galle PR, Kanzler S. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol 2010; 44: 208-213 [PMID: 20087196 DOI: 10.1097/MCG.0b013e3181c74e6d]
15. Longhi MS, Hussain MJ, Kowk WW, Mieli-Vergani G, Ma Y, Vergani D. Autoantigen-specific regulatory T cells, a potential

van Gerven NMF et al. Epidemiology, clinical aspects and treatment
tool for immune-tolerance reconciliation in type-2 autoimmune hepatitis. Hepatology 2011; 53: 536-547 [PMID: 21274874 DOI: 10.1002/hep.24039]

16 Longhi MS, Medina F, Wang P, Samyn M, Mieli-Vergani G, Vergani D. Ma Y. Expansion and de novo generation of potentially therapeutic regulatory T cells in patients with autoimmune hepatitis. Hepatology 2008; 47: 581-591 [PMID: 18220288 DOI: 10.1002/hep.22071]

17 Peiseler M, Sebode M, Franke B, Wortmann F, Schwinge D, Quasas A, Baron U, Olek S, Wiegard C, Lohse AW, Weiler-Norman C, Schramm C, Herkel J. FOXP3 regulatory T cells in autoimmune hepatitis are fully functional and not reduced in frequency. J Hepatol 2012; 57: 125-132 [PMID: 22425700 DOI: 10.1016/j.jhep.2012.02.029]

18 Dalekos GN, Obermayer-Straub P, Bartels M, Maeda T, Kayser D, Lafon B, Smail A, Cévallos R, Chatelain D, Andréjak U, Umemura T, Ota M. Genetic background of autoimmune hepatitis. J Gastroenterol 2015; 50: 125-132 [PMID: 26115588 DOI: 10.1002/jgastro.11046]

19 Obermayer-Straub P, de Boer YS, Zwiers A, Verwer BJ, Drenth JP, van Enk JG, Avis WA. Minocycline-induced autoimmune hepatitis: Genetic factors affecting the occurrence, clinical phenotype, and outcome of autoimmune hepatitis. Clin Gastroenterol Hepatol 2008; 6: 379-388 [PMID: 18328791 DOI: 10.1016/j.cgh.2007.12.048]

20 Doherty DG, Donaldson PT, Underhill JA, Farrant JM, Guthrie JA, Mieli-Vergani G, McFarlane IG, Johnson PJ, Williams R. Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. Hepatology 1991; 13: 701-706 [PMID: 2010165 DOI: 10.1002/hep.1840130415]

21 Montano-Loza AJ, Carpenter HA, Czaja AJ. Clinical significance of HLA DRB1*03-DRB1*04 in type 1 autoimmune hepatitis. Liver Int 2006; 26: 1201-1208 [PMID: 17105585 DOI: 10.1111/j.1478-3231.2006.01387.x]

22 Yoshizawa K, Umemura T, Ota M. Genetic background of autoimmune hepatitis in Japan. J Gastroenterol 2011; 46 Suppl 1: 42-47 [PMID: 20957499 DOI: 10.1007/s00535-010-0332-2]

23 Seki T, Ota M, Furuta S, Fukushima H, Kondo T, Hino K, Mizuki N, Ando A, Tsuji K, Inoko H. HLA class II molecules and autoimmune hepatitis susceptibility in Japanese patients. Gastroenterology 1992; 103: 1041-1047 [PMID: 1354193]

24 Vázquez-Garcia MN, Aláez C, Olivo A, Debaz H, Pérez-Luque E, Burguete A, Cano S, de la Rosa G, Bautista N, Hernández A, Bandera J, Torres LF, Kershenobich D, Alvarez F, Gorodezky C. MHC class II sequences of susceptibility and protection in Mexicans with autoimmune hepatitis. J Hepatol 1998; 28: 985-990 [PMID: 9672174 DOI: 10.1016/S0168-8278(98)80347-4]

25 Czaja AJ, Strettell MD, Thomson LJ, Santrach PJ, Moore SB, Donaldson PT, Williams R. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. Hepatology 1997; 25: 317-323 [PMID: 9021941 DOI: 10.1002/hep.510250211]

26 Czaja AJ, Donaldson PT. Gender effects and synergisms with histocompatibility leukocyte antigens in type 1 autoimmune hepatitis. Am J Gastroenterol 2002; 97: 2051-2057 [PMID: 12190176 DOI: 10.1111/j.1572-0241.2002.05921.x]

27 Czaja AJ. Genetic factors affecting the occurrence, clinical phenotype, and outcome of autoimmune hepatitis. Clin Gastroenterol Hepatol 2008; 6: 379-388 [PMID: 18328791 DOI: 10.1016/j.cgh.2007.12.048]

28 Doherty DG, Donaldson PT, Underhill JA, Farrant JM, Guthrie JA. Mieli-Vergani G, McFarlane IG, Johnson PJ, Edelsten AL, Mowat AP. Allelic sequence variation in the HLA class II genes and proteins in patients with autoimmune hepatitis. Hepatology 1994; 19: 609-615 [PMID: 8119685 DOI: 10.1002/hep.184090311]

29 Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearnry RB, Stedman CA. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010; 25: 1681-1686 [PMID: 20880179 DOI: 10.1111/j.1440-1746.2010.06384.x]

30 van Gerven NM, de Boer YS, Zwieters A, Verwer BI, Drenth JP, van Hoek B, van Erpecum KJ, Beuers U, van Buuren HR, den Ouden JW, Verdonck RC, Koek GH, Brouwer JT, Guichelaar MM, Vrolijk JM, Coenraad MJ, Krala G, Mulder CJ, van Nieuwkerk CM, Bloemen EA, Verspaget HW, Kumar V, Zernakova A, Wijmenga C, Frankle L, Bouma G. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome autoimmune hepatitis type-1. Genes Immun 2015; 16: 247-252 [PMID: 25611558 DOI: 10.1038/gene.2014.82]

31 Agarwal K, Czaja AJ, Jones DE, Donaldson PT. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphisms and susceptibility to type 1 autoimmune hepatitis. Hepatology 2000; 31: 49-53 [PMID: 10613727 DOI: 10.1002/hep.10310101]

32 Fan LY, Tu XQ, Cheng QB, Zha Y, Feltens R, Pfeiffer T, Zhong RQ. Cytotoxic T lymphocyte associated antigen-4 gene polymorphisms confer susceptibility to primary biliary cirrhosis and autoimmune hepatitis in Chinese population. World J Gastroenterol 2004; 10: 3056-3059 [PMID: 15378793 DOI: 10.3748/wjg.v10.20.3056]

33 van Gerven NM, de Boer YS, Zwieters A, van Hoek B, van Erpecum KJ, Beuers U, van Buuren HR, den Ouden JW, Verdonck RC, Koek GH, Brouwer JT, Guichelaar MM, Vrolijk JM, Krala G, Mulder CJ, van Nieuwkerk CM, Bouma G. Cytotoxic T lymphocyte antigen-4 +49A/G polymorphism does not affect susceptibility to autoimmune hepatitis. Liver Int 2013; 33:
van Gerven NM et al. Epidemiology, clinical aspects and treatment

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1039-1043 [PMID: 23551963 DOI: 10.1111/liv.12157]

Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. Hepatology 2007; 46: 2018-2028 [PMID: 17705297 DOI: 10.1002/hep.21884]

Al-Chalabi T, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. J Hepatol 2008; 49: 140-147 [PMID: 18023911 DOI: 10.1016/j.jhep.2007.08.013]

Lohse AW, Gerken G, Mohr H, Löhr HF, Treichel U, Dienes HP, Meyer zum Büschenfelde KH. Relation between autoimmune liver diseases and viral hepatitis: clinical and serological characteristics in 859 patients. Z Gastroenterol 1995; 33: 527-533 [PMID: 8525656]

Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]

Tripathi D, Neuberger J. Autoimmune hepatitis and liver transplantation: indications, results, and management of recurrent disease. Semin Liver Dis 2009; 29: 286-296 [PMID: 19676601 DOI: 10.1055/s-0029-1233531]

Kim BH, Kim YJ, Jeong SH, Tak WY, Ahn SH, Lee YJ, Jung ES, Kwon SY, Cha HB, Kim DJ, Shin SK. Clinical features of autoimmune hepatitis and comparison of two diagnostic criteria in Korea: a nationwide, multicenter study. J Gastroenterol Hepatol 2013; 28: 128-134 [PMID: 23033899 DOI: 10.1111/j.1440-1746.2012.07292.x]

Wong RJ, Gish R, Frederick T, Bezwij N, Fenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J Clin Gastroenterol 2012; 46: 155-161 [PMID: 21814143 DOI: 10.1097/MCG.0b013e3182287b81]

van Gerven NM, Bakker SF, de Boer YS, Witte BI, Bontkes H, van Nieuwkerk CM, Mulder CJ, Bouma G. Seroprevalence of celiac disease in patients with autoimmune hepatitis. Eur J Gastroenterol Hepatol 2014; 26: 1104-1107 [PMID: 25089548 DOI: 10.1111/ejh.12518]

Silveira MG, Lindor KD. Overlap syndromes with autoimmune chronic cholestatic liver diseases. Expert Rev Gastroenterol Hepatol 2007; 1: 329-340 [PMID: 19072425 DOI: 10.1586/17474124.1.2.329]

Boberg KM, Chapman RW, Hirschfeld GM, Lohse AW, Manns MP, Schumpff E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011; 54: 374-385 [PMID: 21067383 DOI: 10.1016/j.jhep.2010.09.002]

Abdalian R, Dhar P, Jha her V, Haider M, Guindi M, Heathcote J. New insights into autoimmune liver diseases. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]

Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]

Wong RJ, Gish R, Frederick T, Bezwij N, Fenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J Clin Gastroenterol 2012; 46: 155-161 [PMID: 21814143 DOI: 10.1097/MCG.0b013e3182287b81]

van Gerven NM, Bakker SF, de Boer YS, Witte BI, Bontkes H, van Nieuwkerk CM, Mulder CJ, Bouma G. Seroprevalence of celiac disease in patients with autoimmune hepatitis. Eur J Gastroenterol Hepatol 2014; 26: 1104-1107 [PMID: 25089548 DOI: 10.1111/ejh.12518]

Silveira MG, Lindor KD. Overlap syndromes with autoimmune chronic cholestatic liver diseases. Expert Rev Gastroenterol Hepatol 2007; 1: 329-340 [PMID: 19072425 DOI: 10.1586/17474124.1.2.329]

Boberg KM, Chapman RW, Hirschfeld GM, Lohse AW, Manns MP, Schumpff E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011; 54: 374-385 [PMID: 21067383 DOI: 10.1016/j.jhep.2010.09.002]

Abdalian R, Dhar P, Jha her V, Haider M, Guindi M, Heathcote J. New insights into autoimmune liver diseases. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]

Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]

Wong RJ, Gish R, Frederick T, Bezwij N, Fenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J Clin Gastroenterol 2012; 46: 155-161 [PMID: 21814143 DOI: 10.1097/MCG.0b013e3182287b81]

van Gerven NM, Bakker SF, de Boer YS, Witte BI, Bontkes H, van Nieuwkerk CM, Mulder CJ, Bouma G. Seroprevalence of celiac disease in patients with autoimmune hepatitis. Eur J Gastroenterol Hepatol 2014; 26: 1104-1107 [PMID: 25089548 DOI: 10.1111/ejh.12518]

Silveira MG, Lindor KD. Overlap syndromes with autoimmune chronic cholestatic liver diseases. Expert Rev Gastroenterol Hepatol 2007; 1: 329-340 [PMID: 19072425 DOI: 10.1586/17474124.1.2.329]

Boberg KM, Chapman RW, Hirschfeld GM, Lohse AW, Manns MP, Schumpff E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011; 54: 374-385 [PMID: 21067383 DOI: 10.1016/j.jhep.2010.09.002]

Abdalian R, Dhar P, Jha her V, Haider M, Guindi M, Heathcote J. New insights into autoimmune liver diseases. Hepat Res Treat 2011; 2011: 390916 [PMID: 21760995 DOI: 10.1155/2011/390916]
27 Qi D, Wang Q, Wang H, Xie Q, Zang G, Jiang H, Tu C, Guo J, Zhang S, Wang J, Lu Y, Han Y, Shen L, Chen X, Hu X, Wang X, Chen C, Fu Q, Ma X. Validation of the simplified criteria for diagnosis of autoimmune hepatitis in Chinese patients. *J Hepatol* 2011; 54: 340-347 [PMID: 21056494 DOI: 10.1016/j.jhep.2010.06.032]

28 Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology* 2005; 42: 53-62 [PMID: 15954109 DOI: 10.1002/hep.20732]

29 Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology* 1996; 110: 848-857 [PMID: 8608895 DOI: 10.1016/gast.1996.v110.pn8608895]

30 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015; 63: 971-1004 [PMID: 26341719 DOI: 10.1016/j.jhep.2015.06.030]

31 Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011; 60: 1611-1629 [PMID: 21757447 DOI: 10.1136/gut.2010.235259]

32 Oo YH, Hubscher SG, Adams DH. Autoimmune hepatitis: new paradigms in the pathogenesis, diagnosis, and management. *Hepatol Int* 2010; 4: 475-493 [PMID: 20827405 DOI: 10.1007/s12072-010-9183-5]

33 Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; 333: 958-963 [PMID: 7666194 DOI: 10.1056/NEJM199510233328102]

34 Lammers MM, van Oijen MG, Pronk M, Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. *J Hepatol* 2010; 53: 191-198 [PMID: 20400196 DOI: 10.1016/j.jhep.2010.01.037]

35 Strassburg CP, Manns MP. Treatment of autoimmune hepatitis. *Semin Liver Dis* 2009; 29: 273-285 [PMID: 19676000 DOI: 10.1055/s-0029-1233554]

36 Stellan AJ, Keating JJ, Johnson PJ, McFarlane IG, Williams R. Maintenance of remission in autoimmune chronic active hepatitis with azathioprine after corticosteroid withdrawal. *Hepatology* 1988; 8: 781-784 [PMID: 3292363 DOI: 10.1002/hep.184080414]

37 Jharap B, Seinen ML, de Boer NK, van Ginkel JR, Linskens RK, Kneppelhout JC, Mulder CJ, van Bodegraven AA. Thiopurine methyltransferase: a new treatment for autoimmune chronic active hepatitis. *J Hepatol* 1997; 27: 332-336 [PMID: 9168893 DOI: 10.1016/S0168-8278(96)80128-1]

38 Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, Schoenfield LJ. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972; 63: 820-833 [PMID: 4538724]

39 Läth S, Herkel J, Kanzler S, Frenzel C, Galle PR, Diem HP, Schramm C, Lohse AW. Serologic markers compared with liver biopsy for monitoring disease activity in autoimmune hepatitis. *J Clin Gastroenterol* 2008; 42: 926-930 [PMID: 18645526 DOI: 10.1097/MCG.0b013e318154ff74]

40 Hartl J, Ehlikken H, Weiler-Norman C, Sebode M, Kreuels B, Pannicke N, Zenouzi R, Glaubke C, Lohse AW, Schramm C. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015; 62: 642-646 [PMID: 25457202 DOI: 10.1016/j.jhep.2014.10.018]

41 Summerskill WH, Kornman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut* 1975; 16: 878-883 [PMID: 1104411 DOI: 10.1136/gut.16.11.876]

42 Czaja AJ, Menon KV, Carpenter HA. Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: a retrospective analysis. *Hepatology* 2002; 35: 890-897 [PMID: 11915036 DOI: 10.1053/jhep.2002.32485]

43 van Gerven NM, Verwer BJ, Witte BL, van Hoek B, Coenraad MJ, van Erpecum KJ, Beuers U, van Buuren HR, de Man RA, Drenth JP, den Ouden JW, Verdonk RC, Koek GH, Brouwer JT, Guichelaar MM, Mulder CJ, van Nieuwkerk KM, Bouma G. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013; 58: 141-147 [PMID: 22989569 DOI: 10.1016/j.jhep.2012.09.009]

44 Yoshizawa K, Matsumoto A, Ichijo T, Umemura T, Yoshizawa K, Abe M, Onji M. Long-term outcome of Japanese patients with type 1 autoimmune hepatitis. *Hepatology* 2012; 56: 668-676 [PMID: 22334246 DOI: 10.1002/hep.25658]

45 Bode GS, van Gerven NM, van Oijen MG, Pronk M, Drenth JP. Treatment of autoimmune hepatitis: a systematic review of randomized controlled trials. *J Med Microbiol* 2010; 59: 12072-010-9183-5

46 Summerskill WH, Baggenstoss AH, Bodek M, Kopp J, Lurie Y, Rust C, Zuckerman E, Bahr MJ, Günther R, Hultcrantz RW, Spengler U, Lohse AW, Szalay F, Färöllk M, Pröls M, Strassburg CP. Budesonide induces remission more effectively than prednisone.
in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010; **139**:1198-1206 [PMID: 20600032 DOI: 10.1053/j.gastro.2010.06.046]

108 *Wojnarowski M*, Nemeth A, Baruch Y, Koletzko S, Melter M, Rodeck B, Strassburg CP, Pröls M, Woźniak M, Manns MP. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. *J Pediatr* 2013; **163**:1347-1453.e1 [PMID: 23810723 DOI: 10.1016/j.jpeds.2013.05.042]

109 *Lees CW*, Maan AK, Hansoti B, Satsangi J, Arnott ID. Tolerability and safety of mercaptopurine in azathioprine-intolerant patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **27**: 220-227 [PMID: 17998235 DOI: 10.1111/j.1365-2036.2007.03570.x]

110 *Hübener S*, Oo YH, Than NN, Hübener P, Weiler-Normann C, Lobse AW, Schramm C. Efficacy of 6-Mercaptopurine as Second-Line Treatment for Patients With Autoimmune Hepatitis and Azathioprine Intolerance. *Clin Gastroenterol Hepatol* 2016; **14**: 445-453 [PMID: 26492846]

111 *de Boer NK*, van Nieuwkerk CM, Aparicio Pages MN, de Boer SY, Derjiks LI, Mulder CJ. Promising treatment of autoimmune hepatitis with 6-thioguanine after adverse events on azathioprine. *Eur J Gastroenterol Hepatol* 2005; **17**: 457-461 [PMID: 15756101 DOI: 10.1097/00042737-200504000-00012]

112 *Herzog D*, Rasquin-Weber AM, Debray D, Alvarez F. Subfulminant hepatic failure in autoimmune hepatitis type 1: an unusual form of presentation. *J Hepatol* 1997; **27**: 578-582 [PMID: 9314137 DOI: 10.1016/S0168-8278(97)80364-9]

113 *Kessler WR*, Cummings OW, Eckert G, Chalasani N, Lameng L, Kwo PY. Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2004; **2**: 625-631 [PMID: 15224287 DOI: 10.1016/S1542-3565(04)00246-0]

114 *Murray-Lyon IM*, Stern RB, Williams R. Controlled trial of prednisone in azathioprine and azathioprine in chronic active hepatitis. *Lancet* 1973; **1**: 735-737 [PMID: 4121073 DOI: 10.1016/S0140-6736(03)70452-X]

115 *Migita K*, Watanabe Y, Jiuchi Y, Nakamura Y, Saito A, Yogura M, Otta H, Shimada M, Mita E, Hijikata T, Yanashita H, Takezaki E, Muro T, Sakai H, Nakamuta M, Abiru S, Komori A, Ito M, Yatsuhashi H, Nakamura M, Ishibashi H. Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization-autoimmune hepatitis prospective study). *Liver Int* 2012; **32**: 837-844 [PMID: 22221966 DOI: 10.1011/j.lig.2011.02734.x]

116 *Czaja AJ*. Hepatocellular carcinoma and other malignancies in autoimmune hepatitis. *Dig Dis Sci* 2013; **58**: 1459-1476 [PMID: 23306849 DOI: 10.1007/s10620-012-2525-5]

117 *Teufel A*, Weinmann A, Centner C, Pendl A, Lobse AW, Galle PR, Kanzler S. Hepatocellular carcinoma in patients with autoimmune hepatitis. *World J Gastroenterol* 2009; **15**: 578-582 [PMID: 19195059 DOI: 10.3748/wjg.v15.i7.578]

118 *Werner M*, Almer S, Prytz H, Lindgren S, Wällerstedt S, Björnsson E, Bergquist A, Sandberg-Gertzen H, Hultcrantz R, Sangl F, Weiland O, Danielsson S. Hepatic and extrahepatic malignancies in autoimmune hepatitis. A long-term follow-up in 473 Swedish patients. *J Hepatol* 2009; **50**: 388-393 [PMID: 19070390 DOI: 10.1016/j.jhep.2008.08.022]

119 *Yeoman AD*, Al-Chalabi TA, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, Bombordi A, O’Grady JG, Harrison PM, Heneghan MA. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. *Hepatology* 2008; **48**: 863-870 [PMID: 18752332 DOI: 10.1002/hep.22432]

120 *Malekzadeh Z*, Haghazali S, Sepanlou SG, Vahedi H, Merat S, Soutedeh M, Nasseri-Moghaddam S, Malekzadeh R. Clinical features and long term outcome of 102 treated autoimmune hepatitis patients. *Hepat Mon* 2012; **12**: 92-99 [PMID: 22509185 DOI: 10.5812/hepatmon.4906]

121 *Cross TJ*, Antoniades CG, Muiesan P, Al-Chalabi T, Aluvihare V, Agarwal K, Portmann BC, Rela M, Heaton ND, O’Grady JG, Heneghan MA. Liver transplantation in patients over 60 and 65 years: an evaluation of long-term outcomes and survival. *Liver Transpl* 2007; **13**: 1382-1388 [PMID: 17902123 DOI: 10.1002/lit.21181]

122 *Vogel A*, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, Klemmnauer J, Basham B, Manns MP, Strassburg CP. Long-term outcome of liver transplantation for autoimmune hepatitis. *Clin Transplant* 2004; **18**: 62-69 [PMID: 15108772 DOI: 10.1111/j.1399-0012.2004.00117.x]

123 *Seaberg EC*, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in the United States from 1987-1998: updated results from the Pitt-UNOS Liver Transplant Registry. *Clin Transpl* 1998; **17-18** [PMID: 10503083]

124 *Liberal R*, Longhi MS, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis after liver transplantation. *Clin Gastroenterol Hepatol* 2012; **10**: 346-353 [PMID: 22056300 DOI: 10.1016/j.cgh.2011.10.028]

125 *Whalley S*, Puvanachandra P, Desai A, Kennedy H. Hepatology outpatient service provision in secondary care: a study of liver disease incidence and resource costs. *Clin Med (Lond)* 2007; **7**: 119-124 [PMID: 17491498 DOI: 10.7861/clinmedicine.7-2-119]

126 *Delgado JS*, Vodonos A, Malnick S, Kriger O, Wilkof-Segev R, Delgado B, Novack V, Rosenthal A, Menachem Y, Melzer E, Fich A. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. *J Dig Dis* 2013; **14**: 611-618 [PMID: 23815477 DOI: 10.1111/j.1751-2980.2012.00853.x]

127 *Primo J*, Merino C, Fernández J, Molés JR, Llorca P, Hinojosa J. Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain). *Gastroenterol Hepatol* 2004; **27**: 239-243 [PMID: 15056409 DOI: 10.1016/S0210-5705(03)70452-X]

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