Autoimmune Hepatitis: Factors Involved in Initiation and Methods of Diagnosis and Treatment

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ABSTRACT: Autoimmune hepatitis is an acute or mostly chronic liver disease that can affect both adults and children and has a clear prevalence for the female sex. A definite etiology has not been established, but it is known that genetic predisposing profiles and exogenous trigger factors are involved. The main diagnostic criteria include typical histological features, the occurrence of serum auto-antibodies, and increased levels of transaminases and gamma-globulins. Instances of autoimmune hepatitis sharing features with other autoimmune liver diseases have also been observed. An imbalance of the immune system with persistent activation of effector T cells has been emphasized to account for the sustained liver injury. Clinical manifestations are variable both at presentation and throughout the course of the disease, ranging from an asymptomatic state or the occurrence of non-specific symptoms to the features of end-stage liver disease such as jaundice, ascites, and gastrointestinal bleeding. A clinical and biochemical remission is achieved in at least 80% of patients receiving corticosteroids with or without the addition of azathioprine. Alternative therapeutic schedules have been proposed for unresponsive and intolerant patients. Given that relapse often occurs after therapy withdrawal, maintenance treatment is usually required.

KEY WORDS: autoimmune hepatitis, anti-nuclear antibodies, anti-smooth muscle antibodies, anti-LKM antibodies, corticosteroids, immunosuppressive drugs

ABBREVIATIONS: AIH, autoimmune hepatitis; AILD, autoimmune liver disease; AISC, autoimmune sclerosing cholangitis; ALT, alanine transaminase; ANCA, anti-neutrophil cytoplasmic antibody; ANA, anti-nuclear antibody; APC, antigen-presenting cell; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy; ASGP-R, asialoglycoprotein receptor; CTLA-4, cytotoxic T lymphocyte antigen-4; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLA, human leukocyte antigen; IAIHG, International Autoimmune Hepatitis Group; IFN, interferon; IL, interleukin; LC, liver cytosol; LKM, liver–kidney microsomal; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; pANNA, peripheral anti-nuclear neutrophil antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA/LP, soluble liver antigen/liver pancreas; SMA, smooth muscle auto-antibody; TCR, T-cell receptor; Th, T helper; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase; Treg, regulatory T cell; ULN, upper limit of normal

I. HISTORY AND DEFINITION

In 1950, Jan Waldenström first recognized the case of a young woman with hepatic dysfunction associated with hypergammaglobulinemia as a possible “new” liver disease.1 Kunkel et al. in 1951 confirmed the occurrence of hypergammaglobulinemia in 11 young women with liver disease associated with plasma cell infiltration in the liver.2 In 1956, based on the demonstration of serum anti-nuclear antibodies (ANAs) and the occurrence of the so-called lupus erythematosus cells, the term “lupoid hepatitis” was introduced and an altered immunological tolerance was hypothesized in the pathogenesis of certain types of chronic active hepatitis.3 Mackay et al. firstly proposed the term “autoimmune hepatitis” in 1965.4 An important step forward was the demonstration in 1973 of the efficacy of corticosteroids and immunosuppression in the treatment of this clinical entity, still defined as
“active chronic hepatitis.” After the establishment of the International Autoimmune Hepatitis Group (IAIHG), the term “autoimmune hepatitis” (AIH) was adopted definitively.

According to currently available guidelines, AIH is defined as a liver inflammation of unknown origin characterized by a frequently insidious onset, non-specific symptoms (fatigue, nausea, abdominal pain, arthralgias) and a wide clinical spectrum ranging from an asymptomatic presentation to severe acute hepatitis. The diagnostic algorithm includes typical histological features, polyclonal hypergammaglobulinemia, and the occurrence of non-organ-specific auto-antibodies. As described later, two or possibly three types of AIH can be recognized, in which a T-cell-mediated liver damage can evolve into a necro-inflammatory and fibrotic process.

The more extensive term “autoimmune liver disease” (AILD) includes a complex spectrum of pathological conditions affecting both hepatocytes and cholangiocytes and leading to liver cirrhosis and end-stage liver disease. Although AIH is the typical AILD affecting hepatocytes, primary biliary cholangitis (PBC) is the most common cholestatic and primary sclerosing cholangitis (PSC) a more rare, cholestatic AILD with poor response to therapy. “Variant forms,” characterized by the coexistence of immunological and histological features of two conditions, can also be observed; in these cases, which lack well-defined diagnostic criteria, patients should be categorized according to the primary clinical and histological disease manifestations with additional features of the other condition(s) (i.e., PBC with features of AIH).

Among AILDs, a brief mention should also be made of autoimmune sclerosing cholangitis (AISC) in children, which often has a severe course, is frequently associated with inflammatory bowel disease, and may be ascribable to different etiologies. Autoimmune features similar to those of AIH occur in the large majority of the patients. Increased serum IgG4 levels can be detected in approximately 15% of the patients, but they cannot be differentiated from AISC patients with normal IgG4 levels in terms of clinical and/or imaging features. Although immunosuppression usually results in a good biochemical response, the involvement of bile duct may progress and eventually require liver transplantation. Severity of liver disease and risk of recurrence after transplant are linked to extension and severity of bowel disease.

The aim of this review is to provide an updated narrative of the main epidemiological, clinical, pathogenetic, and therapeutic features of AIH.

II. EPIDEMIOLOGY

The prevalence of AIH is still poorly defined given the low number of population-based studies and the lack of standardized diagnostic criteria, especially with reference to the studies published before the introduction of a scoring system by the IAIHG.

AIH affects both sexes, has a strong female prevalence (about 4:1 for type 1 and 10:1 for type 2), and can be diagnosed at all ages from infants to the elderly population. A bimodal age distribution was reported initially, with a first peak at 10–30 years and a second peak at 40–50 years, but AIH is increasingly recognized also in patients older than 60–65 years. Examples of AIH epidemiology in different countries are summarized in Table 1. The highest prevalence (42.9/100,000 including definite or probable AIH) has been reported in the Alaskan population. In Norway and Sweden, a prevalence of 11 and 17 per 100,000, respectively, has been reported. In a Danish nationwide, population-based study on AIH patients identified from healthcare registries over a period of 18 years, an increasing incidence has been detected from 1.37/100,000/year in 1994 to 2.33 in 2012, with a prevalence of 23.9/100,000 at the end of 2012. This study has confirmed the disease prevalence in the female sex and has identified male sex and cirrhosis as adverse prognostic factors. In New Zealand, a similar result with female predominance and a prevalence of 24.5/100,000 was found. An incidence of 0.83/100,000/year and a prevalence of 11.6 cases per 100,000 has been reported in a Spanish population. Although an approximately similar prevalence rate has been described in southern Israel, AIH appears to be less frequent in Eastern countries. In Japan, for example, the incidence ranges from 0.015 to 0.08 for type 1 AIH.
and a low incidence has been similarly reported in China, although it seems to increase as more definite diagnostic criteria are applied.\textsuperscript{27}

A great geographic variability in AIH has been shown in terms of clinical manifestations, severity of disease, and outcome. For example, whereas African-American patients frequently develop cirrhosis,\textsuperscript{28} African and Asian patients prevalently exhibit a cholestatic pattern compared with patients of European Caucasoid ethnic origin.\textsuperscript{29} In Japan, patients display a late-onset disease that usually requires less aggressive immunosuppressive therapies.\textsuperscript{30}

III. ETIOLOGY AND PATHOGENESIS

The etiology of AIH remains unknown. Several factors possibly contribute to the onset of the disease, including genetic and environmental factors, as well as a dysregulation of the immune system. The variability in terms of clinical features and outcomes in AIH patients of different ethnic groups probably reflects genetic predispositions and different local etiological factors.\textsuperscript{31} The genetic predisposition to type 1 AIH is mainly related to human leukocyte antigen (HLA) class II genes.\textsuperscript{32} Although these genes located on the short arm of chromosome 6 are those of the major histocompatibility complex (MHC) involved in antigen presentation to T cells, they cannot completely explain AIH predisposition, which likely requires the action of additional genes and/or environmental factors.\textsuperscript{32}

The most stringent associations have been found within the HLA-DRB1 locus (DRB1*0301 encoding HLA-DR3 and DRB1*0401 encoding HLA-DR4) in European and North American populations.\textsuperscript{33} In Italy, however, HLA-DR4 does not seem to be associated with AIH.\textsuperscript{34} On the contrary, HLA-DR3 is rare in the normal Japanese population and 75% of AIH patients were found to be positive for HLA-DR4.\textsuperscript{35} This antigen also characterizes the Korean and Argentine adult populations\textsuperscript{36}: DRB1*1301 in Argentinian children and Brazilians and DRB1*0404 in Mexicans. DRB1*0301 alleles are apparently related to worse clinical outcome despite corticosteroid treatment.\textsuperscript{37} In type 2 AIH, DRB1*0301 and DRB1*0701 encoding alleles seem to be associated with higher susceptibility and severity of disease. In addition, variations within HLA-DRB1 alleles may influence auto-antibody expression.\textsuperscript{38}

AIH susceptibility may also be influenced by non-HLA gene variability. In Caucasian patients with type 1 AIH, cytotoxic T lymphocyte antigen-4 (CTLA-4) polymorphisms have been described.\textsuperscript{39} In the Japanese population, promoter polymorphisms of Fas were found to influence AIH susceptibility, whereas in Caucasians, they affect the early development of cirrhosis.\textsuperscript{40,41}

More recently,\textsuperscript{42} a genome-wide approach was used to identify genetic variants that may predispose to type 1 AIH in a cohort of patients from the Netherlands, Germany, and Switzerland. The results showed a strong association between AIH

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence (n/100,000)</th>
<th>Incidence (n/100,000/year)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
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<td>–</td>
<td>19</td>
</tr>
<tr>
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<td>20</td>
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</tr>
<tr>
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<tr>
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<td>11.6</td>
<td>0.83</td>
<td>24</td>
</tr>
<tr>
<td>Israel</td>
<td>11</td>
<td>0.67</td>
<td>25</td>
</tr>
<tr>
<td>Japan</td>
<td>–</td>
<td>0.015–0.08</td>
<td>26</td>
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</tbody>
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TABLE 1: Examples of the variable epidemiology of AIH in different countries
and a genetic variant in the MHC region in the Netherlands. HLA-DRB1*0301 has been identified as a primary and HLA-DRB1*0401 as a secondary susceptibility genotype. Outside of MHC, variants of the SH2B3 (rs3184504, 12q24) gene, encoding for a missense variant in exon 3 of the Scr homology 2 adaptor protein 3, and caspase recruitment domain family member 10 (CARD10-rs6000782, 22q13.1) gene, have been identified as probable risk factors. The presence of the rs3184504 allele correlated with a concomitant autoimmune disease, but not with age of onset, serum IgG, or alanine transaminase (ALT) levels, whereas the rs6000782 allele was not associated with any of these clinical features.42

HLA-DRB1*0301 was associated with an earlier age of onset, higher IgG levels at AIH presentation, and other concomitant autoimmune diseases, whereas HLA-DRB1*0401 was the opposite. These data confirmed previous reports in small groups of Caucasian patients.37,43

MHC class II molecules are expressed on the surface of antigen-presenting cells (APCs), primarily presenting exogenous antigens to CD4+ cells. Exogenous antigens may trigger an immune response directed to similar endogenous antigens, thus defining the molecular mimicry that has been proposed as a potential pathogenetic mechanism in the development of AILD.32 In this context, several environmental factors have been proposed as potential triggers in AILD. Among them, viruses such as Epstein–Barr virus (EBV), other herpes simplex viruses, hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus have been associated with the development of AIH. For example, HCV seems to share a high amino-acid sequence homology with cytochrome P4502D6 (CYP2D6), which is the auto-antigenic target of anti-liver–kidney microsomal (LKM)-1 auto-antibodies typical of type 2 AIH.43 CYP2A6 was also identified as another hepatic auto-antigen.45 Moreover, a potential role in inducing AIH has been reported to be played by interferon (IFN)-based antiviral treatments against HCV chronic infection.46 Notably, EBV has been involved in several autoimmune disorders due to its high prevalence worldwide, its persistence in the host B lymphocytes and its ability to affect the immune response. Some observations report the development of AIH after EBV infection,47,48 but comprehensive studies linking EBV infection to AIH are still lacking.49

Epitope spreading or exposure to auto-antigens released as a consequence of hepatocyte damage have been proposed as possible additional pathogenetic mechanisms.50,51 Epitope spreading was first described in type 2 AIH, in which CYP2D6 is the main target of anti-LKM-1 auto-antibodies, while analyzing the anti-CYP2D6 antibody response over a prolonged period of time both in patients and in a mouse model.50 In both cases, the humoral immune response was directed to an immunodominant epitope, later expanding to neighboring and remote regions, suggesting that molecular mimicry is an initiating event.52 Because enzymes represent the majority of liver-specific auto-antigens (e.g., CYP450s), it has been hypothesized that they could be released after liver injury (viral triggered or drug induced), even if this hypothesis does not account for the extreme specificity of auto-antibodies.53

Among non-viral potential triggers, drugs such as nitrofurantoin, minocycline, statins, and the anti-tumor necrosis factor (TNF) agents infliximab and adalimumab have been recognized.54–58 Additional drugs that have been studied are tienilic acid, pemoline, melatonin, ornidazole, diclofenac, propythiouracil, and some herbal remedies in common use in Japan.17,59–65 Three possible clinical scenarios can be described: (1) drug-induced liver injury (DILI) with a strong immunoallergic component mimicking AIH; (2) AIH resembling DILI due to recent drug exposure and spontaneous regression after drug discontinuation; and (3) AIH triggered by a drug (DILI-induced AIH).7 Drug-induced AIH displays clinical and histological patterns quite similar to genuine AIH, but usually with lower histological activity and without the necessity of a long-term immunosuppression.54 Differentiation between DILI and AIH is often difficult because DILI lacks a reliable diagnostic test and the diagnosis is usually based on clinical and serological findings. However, some histopathological differences have been reported to formulate a more correct diagnosis.66

Although a unique triggering factor cannot be identified, the autoimmune process likely involves different effector cells that are not counterbalanced
by immunoregulatory mechanisms. Figure 1 summarizes the main predisposing and pathogenetic mechanisms that are believed to play a role in AIH. The first proposed event is the presentation of self-antigens to the T-cell receptor (TCR) of uncommitted T-helper lymphocytes (Th0) by professional APCs, including macrophages, dendritic cells and B lymphocytes present in the liver, as well as liver sinusoidal endothelial cells and Kupffer cells.

As a consequence of antigen presentation, the following step is the activation of Th0 cells into Th1 cells in the presence of interleukin 12 (IL-12), Th2 cells in the presence of interleukin 4 (IL-4), and Th17 cells in the presence of interleukin 17 (IL-17), IL-22, and TNF-α.

**FIG. 1:** Main predisposing factors and pathogenetic mechanisms of liver damage in AIH. Exogenous antigens acting as trigger factors (viruses, drugs, others?) in patients with genetic predisposition may induce the emergence of self-antigens (self-Ag), presented by APCs within class II MHCs in the context of an impaired immune regulation. Subsequent differentiation of uncommitted Th0 lymphocytes into Th1, Th2, and Th17 cells is regulated by different cytokines (IL-12, IL-4, IL-6, IL-1β). Th1 cells, in the presence of IL-2 and IFN-γ, activate CD8+ T lymphocytes, which in turn produce IFN-γ and TNF-α. This results in promotion of cytotoxicity based on antigen recognition by class I MHC complex, monocyte differentiation, macrophage and dendritic cell (DC) activation, natural killer (NK) cell killing, upregulation of MHC class I molecules, and aberrant expression of class II MHC molecules on hepatocytes. Conversely, differentiated Th2 cells, in the presence of IL-4, IL-10, and IL-13, stimulate B-cell maturation into plasma cells (PC) that secrete auto-antibodies. Th17 cells may also play a pathogenetic role in the sustained liver damage through the production of IL-17, IL-22, and TNF-α.
presence of IL-4, or Th17 in case of predominance of IL-6 or IL-1β. Th1 cells stimulate the production of IL-2 and IFN-γ and activate CD8-positive T lymphocytes, which in turn produce IFN-γ and TNF-α and promote cytotoxicity based on antigen recognition by class I MHC complex. IFN-γ also induces monocyte differentiation, macrophage and dendritic cell activation, and killing by natural killer cells. In addition, IFN-γ upregulates MHC class I molecules and favors the aberrant expression of MHC class II molecules on hepatocytes that further activate T-cells, thus sustaining liver damage.

Differentiated Th2 cells secrete IL-4, IL-10, and IL-13, which stimulate B-cell maturation into plasma cells, thus promoting auto-antibody production with titers that usually correlate with disease severity. Although the role of Th17 cells has been recognized in PBC, they may also play a pathogenetic role in AIH by producing IL-17, IL-22, and TNF-α. In addition, they induce hepatocytes to secrete IL-6, which enhances Th-17 activation. The possible pathogenetic role of δ-T cells has been reviewed recently. Approximately 15–25% of T cells in the liver express γδ-TCR. These cells may be protective as well as pathogenic in liver diseases in relation to the involved subset identifiable by the expression of TCR chains and the release of specific cytokines. For example, IL-17-expressing γδ-T cells can down-regulate the pathogenic effects of other immune cells such as natural killer T cells. Conversely, these cells in AIH can release granzyme B and IFN-γ, the levels of which seem to correlate with liver damage.

In normal conditions, there is a balance between regulatory and effector cells, leading to tolerance toward liver auto-antigens. Conversely, an impairment of immune regulation should be envisaged in AIH. Autoreactive T-cell clones may emerge from thymus as a consequence of mutations of the autoimmune regulator-1 (AIRE-1) gene, resulting in autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED), a multiorgan disease that includes an autoimmune liver disease such as AIH in 15–20% of cases. In addition, regulatory T cells (Tregs) seem to play an important role in peripheral immune suppression. Natural Tregs originate in the thymus alongside effector T cells, whereas induced Tregs originate in the periphery. Tregs should be better defined as CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup>FOXP3<sup>+</sup> cells and their impairment has been described in different autoimmune diseases including AIH.

Tregs obtained from patients with AIH at diagnosis have shown a reduced capability of modulating CD4 and CD8 effector cells compared with Tregs obtained from patients with AIH at remission or from healthy controls. However, whether the loss of immune tolerance in AIH is the result of a numerical and/or functional defect of Tregs is still unknown. In 2012, Peiseler et al. did not find an impairment of frequency and function of circulating Treg cells defined as CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup> in AIH. More recently, a possible role of CD39-expressing Tregs has been described. CD39 is an ectonucleotidase involved in extracellular nucleotide hydrolysis, inducing the production of adenosine with immunosuppressive properties. In AIH, CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup>FOXP3<sup>+</sup>CD39<sup>+</sup> Tregs have been found to be reduced in number and failed to inactivate IL-17 production by effector CD4 T cells. The same cells have shown an instability to pro-inflammatory stimuli, probably inducing an increased rate of conversion of Tregs into effector cells. This interesting research area requires further investigations to define the most appropriate markers to characterize Tregs cells and their role in AIH.

A potential pathogenetic role has been identified for auto-antibodies against the fibronectin type III domain of the IL4 receptor (CD124), which is expressed on the surface of both lymphocytes and hepatocytes. Such antibodies, identified in type 1 AIH in the majority of cases, might compete with IL4 for receptor binding on hepatocytes, thus interfering with a potential anti-inflammatory role of STAT6 and favoring the development of ectopic lymphoid tissues involved in autoimmunity and inflammation.

An additional T-cell-mediated mechanism seen in AIH is a reduced responsiveness of effector cells. Compared with healthy subjects, in whom inhibitory receptors such as CD5, CTLA-4, and programmed cell death protein-1 (PD-1) are more expressed on the surface of effector T cells, a reduced expression of such receptors such as T-cell immunoglobulin and mucin domain containing molecule 3 (Tim-3) has
been described in AIH.\textsuperscript{85} Interestingly, a remarkable loss of intrahepatic Tregs has been demonstrated in patients with type 1 AIH after immunosuppressive therapy with steroids and azathioprine, a finding that may account for the high relapse rate after drug discontinuation.\textsuperscript{86}

Few animal models are available for the study of AIH. After the identification of CYP2D6 as the molecular target of anti-LKM-1 auto-antibodies in type 2 AIH, a model to induce AIH in mice has been proposed.\textsuperscript{87} According to this model, a chronic hepatitis with histologic features compatible with AIH developed in mice after inoculation of adenovirus vector expressing human CYP2D6. Similarly, another murine model resembling type 2 AIH has been generated by DNA immunization against formimino-transferase cyclodeaminase, an auto-antigen recognized by anti-liver cytosol (LC)-1 auto-antibodies inducing liver injury probably due to molecular mimicry.\textsuperscript{88} Male resistance to the development of type 2 AIH in the same model was ascribed to peripheral tolerance and development of regulatory T cells rather than sexual hormones or central tolerance.\textsuperscript{89}

Neonatal thymectomy in PD-1(–/–) mice induce the loss of naturally arising Treg cells that, in the absence of the PD-1-mediated regulatory pathway, promotes the production of antinuclear auto-antibodies and the development of fatal liver damage characterized by parenchymal CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cell infiltration with severe lobular necrosis.\textsuperscript{90} In the same mouse model, increased serum levels of TNF-\(\alpha\) probably sustain an enhanced hepatic CCL20 expression, thus causing the development of AIH by the CCR6-CCL20 axis-dependent migration of dysregulated splenic T cells. The administration of an anti-TNF-\(\alpha\) suppressed hepatic CCL20 expression, but did not prevent splenic T-cell activation, whereas the administration of an anti-CCL20 suppressed AIH, but did not affect serum TNF-\(\alpha\) levels.\textsuperscript{91}

IV. CLINICAL FEATURES

Clinical manifestations of AIH are variable both at presentation and throughout the course of the disease. In the majority of cases, non-specific symptoms such as fatigue, anorexia, abdominal pain, weight loss, arthralgias, itching, and nausea characterize the disease onset in adult patients. However, approximately one-third of patients are asymptomatic at diagnosis.\textsuperscript{21,22,92,93} In addition, AIH can arise as end-stage liver disease in approximately 30% of cases and present with gastrointestinal bleeding or hypersplenism, even in patients without previous diagnosis of liver disease.\textsuperscript{21,94} Elderly patients are more likely to be cirrhotic and asymptomatic at presentation, associated with HLA-DR4 positivity.\textsuperscript{92} Approximately 25% of patients are diagnosed after routine blood tests showing abnormal liver function.\textsuperscript{94} An acute onset of AIH has been described in approximately 25% of the patients, in whom it could represent an exacerbation of an undiagnosed chronic AIH rather than a truly acute AIH without the histological marks of chronic hepatitis.\textsuperscript{85,95} Furthermore, 30–40% of patients with indeterminate acute liver failure show the clinical, serological, and histological features of autoimmune disease.\textsuperscript{97} Fulminant hepatic failure has been described only rarely.\textsuperscript{98}

The onset of AIH is quite unusual during pregnancy, but it is more probable after delivery (usually within 3 months). In addition, patients with known AIH may show an improvement or a spontaneous remission of liver disease during pregnancy. Conversely, clinical flares with hyper-transaminasemia and hyper-gamma-globulinemia with selective IgG increase can be observed after delivery, probably due to reconstitution of immune system.\textsuperscript{99,100} Immunosuppressive treatment throughout pregnancy is relatively safe and contributes significantly to a reduction of disease flares.\textsuperscript{101}

Of particular importance in the definition of grading and staging of liver disease at diagnosis is liver biopsy. It can detect the presence of cirrhosis in at least one-third of patients, can help to differentiate AIH from other AILD, and is useful to diagnose variant forms. Liver biopsy can also be performed in spontaneously or pharmacologically remitting patients to assess the reversion of histological features to normal conditions or the restriction of inflammation to portal areas.\textsuperscript{102} Although not specific, the histopathological features that characterize AIH are mononuclear cell infiltrates extending beyond the limiting plate, namely the hepatocyte boundary.
surrounding the portal triad, and permeating the surrounding parenchyma. This configuration is defined as interface hepatitis (also known as periportal infiltrate or piecemeal necrosis) and can progress into lobular hepatitis (Fig. 2A).

Another distinguishing feature of AIH is the prominent presence of plasma cells in the infiltrates, thus explaining the definition of “plasma-cell hepatitis” used in the past. However, 34% of patients have few or no portal or acinar plasma cells and this does not exclude the diagnosis of AIH. Although the biliary tree is usually not involved, fibrosis is always present (with the exception of the mildest forms), resulting in cirrhosis in advanced disease. Emperipolesis (active penetration by one cell into and through a larger cell) and hepatic rosette formation are further typical findings that characterize liver histology in AIH and are included into simplified criteria for the diagnosis of AIH.

The clinical course of AIH is often characterized by fluctuating activity. Furthermore, other autoimmune diseases can occur in association with or emerge during the follow-up of AIH. The most frequent are thyroiditis, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, and celiac disease. In approximately 40% of cases, the possibility of autoimmune disorders in first-degree relatives has been reported.

The natural history of AIH has been remarkably modified by conventional treatment with steroids and immunosuppressive drugs. A 10-year survival rate of approximately 80% has been described, strikingly different from a mortality rate of approximately 40% at 6 months from diagnosis reported in the early 1970s. Complications are similar to those characterizing any other progressive liver disease and include cirrhotic evolution and malignant transformation into hepatocellular carcinoma (HCC). HCC can occur in 4% of patients with type 1 AIH, with a 10-year probability of 2.9%. In addition, HCC development has been observed in cirrhotic patients with a rate of 1–2% per year; however, although it occurs less frequently in AIH than in viral hepatitis, an adequate surveillance is obviously recommended in all currently available guidelines. Furthermore, AIH can occur in patients with concomitant liver diseases. A retrospective study evaluating AIH in patients with chronic HBV (including HDV co-infection) and HCV infection showed that HCV-positive patients developed cirrhosis with higher frequency than those with HBV-related disease. In patients with HCV and HBV/HDV chronic infection, AIH was associated with IFN therapy, whereas a better outcome was observed in chronic HBV patients. More recently, it has been reported that patients with coincident AIH and non-alcoholic steatohepatitis develop liver cirrhosis more frequently than patients with AIH alone. In addition, they had a higher relative risk for liver-related mortality and an adverse clinical outcome with decreased survival.

V. LABORATORY FINDINGS AND DETECTION OF AUTO-ANTIBODIES

As expected, the usual biochemical profile of AIH includes increased serum levels of bilirubin and aminotransferases (AST and ALT), ranging from values just above the upper limit of normal (ULN) to more than a 10- to 20-fold increase. Gamma-glutamyl-transpeptidase, but not alkaline phosphatase, can also be increased, although it returns to normal levels after treatment-induced remission. Reflecting the serum elevation of the electrophoretic gammaglobulin fraction, serum IgG levels are also increased, a distinctive feature from serum IgA and IgM that are usually normal. Some investigators have also suggested a possible clinical significance of lower C4 complement fraction levels that characterize patients with AIH probably as a genetically determined predisposing factor.

The detection of auto-antibodies is a key diagnostic criterion in AILD. All currently available scoring systems are based on the different auto-antibody expression, the evaluation of which should be performed in all patients with cryptogenetic hepatitis. Auto-antibodies against nuclear antigens, smooth muscle, LKM-1, and LC-1 are representative of AIH. As a rule, ANAs and/or anti-smooth muscle auto-antibodies (SMAs) test positive in type
FIG. 2: Representative photographs of liver histology and auto-antibody reactivity in AIH. (A) Typical interface hepatitis (piecemeal necrosis) with extension of inflammatory cells into the lobules; few plasma cells are present in the portal tract (hematoxylin & eosin, 200×). (B) ANA homogeneous pattern on rodent kidney section. (C) Anti-SMA reaction on rodent kidney substrate depicting a VGT pattern. (D) anti-LKM-1 reactivity on rodent liver section. (E) Anti-LKM-1 reactivity on rodent kidney section. (F) Detection of anti-LC-1/SLA on rodent liver section.
AIH, whereas anti-LKM-1 and/or anti-LC-1 auto-antibodies are commonly detected in type 2 AIH. These serological abnormalities can be present simultaneously only in rare patients whose clinical course resembles type 2 AIH. Additional auto-antibodies include anti-formimino-transferase-cyclodeaminase, anti-filamentous actin, and atypical peripheral anti-neutrophil cytoplasmic antibodies (ANCAs), which occur more frequently in PSC.

Table 2 summarizes the main auto-antibodies that characterize the different types of AIH, the laboratory methods for their detection, the immunostaining pattern, and the molecular target of each auto-antibody. ANAs are detectable by immunofluorescence on different substrates (i.e., rodent kidney, stomach, and liver). They commonly show a homogeneous or fine speckled pattern (Fig. 2B). Several molecular targets of ANA have been identified, such as single and double-stranded DNA, small nuclear ribonucleoproteins, centromeres, histones, cyclin A, and chromatin, although none of them can be considered specific. The use of Hep-2 cells (with large nuclei and mitotic phase with evident centromere) as the substrate can also be considered. The homogeneous pattern is more typical of type 1 AIH, whereas multiple nuclear dots and rim-like membranous patterns are more typical in PBC.

SMAs are a second class of auto-antibodies that characterize AIH. In 1965, Johnson et al. first described the presence of antibodies reacting to smooth muscle of rat stomach in sera of patients with chronic liver diseases. SMAs can also be detected on substrates such as rodent kidney, stomach, liver, and kidney. They commonly show a homogeneous or fine speckled pattern (Fig. 2B). Several molecular targets of SMA have been identified, such as actin and non-actin (tubulin, vimentin, desmin) cytoskeleton components.

**Table 2: Auto-antibodies in patients with AIH**

<table>
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<tr>
<th>Auto-antibody</th>
<th>Method of detection*/substrates</th>
<th>Immunostaining pattern</th>
<th>Molecular target</th>
<th>Type of AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>IF/rodent kidney, stomach, and liver; Hep-2 cells</td>
<td>Homogeneous/fine speckled pattern</td>
<td>ssDNA; dsDNA; snRNP; centromeres; histones; cyclin A; chromatin</td>
<td>Type-1</td>
</tr>
<tr>
<td>SMA</td>
<td>IF/rat stomach; rodent stomach, liver, and kidney</td>
<td>V (vessels), G (glomeruli), T (tubular) on renal substrates</td>
<td>Actin and non-actin (tubulin, vimentin, desmin) cytoskeleton components</td>
<td>Type-1 (usually VG or VGT pattern)</td>
</tr>
<tr>
<td>LKM</td>
<td>IF/P3 portion of renal tubules and hepatocyte cytoplasm</td>
<td>LKM-1; LKM-2; LKM-3; liver microsomal</td>
<td>Cytochrome P450 IId6 (CYP2D6); cytochrome P4502C9 (CYP2C9); UDP-glucuronosyltransferases; cytochrome P4501A2 (CYP1A2)</td>
<td>Type-2 (LKM-1)</td>
</tr>
<tr>
<td>LC1</td>
<td>IF, ELISA, immunoblot hepatocyte cytoplasm</td>
<td>Cytoplasmatic except centrilobular area</td>
<td>Formimino-transferase cyclodeaminase (FTCD)</td>
<td>Type-2</td>
</tr>
<tr>
<td>Anti-SLA/LP/anti-SEPSECS</td>
<td>RIA-ELISA</td>
<td>Not applicable</td>
<td>Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase</td>
<td>Type-3</td>
</tr>
<tr>
<td>Perinuclear ANCA/pANNA</td>
<td>IF/nuclear membrane components</td>
<td>Perinuclear</td>
<td>(Peripheral) nuclear membrane</td>
<td>Non-specific, unusual in type-2</td>
</tr>
</tbody>
</table>

*IF, immunofluorescence; RIA, radio-immunosorbent assay.
Autoimmune Hepatitis

and liver. The use of renal substrate defines V (vessels), G (glomeruli), and T (tubular) patterns. VG and VGT patterns are considered more common in AIH than the isolated V pattern (Fig. 2C). Targets of SMAs are different structures of the cytoskeleton, including actin and non-actin components (tubulin, vimentin, desmin, skeleton).

Anti-LKMs were first described by Rizzetto et al., whereas Homberg et al. defined anti-LKM-1 as characterizing a different serological type of AIH. The P3 portions of renal tubules and hepatocyte cytoplasm are stained by anti-LKM-1 (Figs. 2D, 2E), the molecular target of which has been shown to be cytochrome P450 IID6 (CYP2D6). Other immunofluorescence reactivities have been recognized in several pathological conditions, including drug-induced hepatitis. Anti-LKM2 auto-antibodies recognize cytochrome P4502C9 (tienilic acid modified epitopes) as a molecular target. Anti-LKM3 auto-antibodies were described for the first time in patients with chronic HDV infection and occasionally also in HCV-positive patients, supporting virus-induced autoimmunity. These antibodies target the UDP-glucuronosyl-transferases and can be found in approximately 10% of type 2 AIH. Variant liver microsomal auto-antibodies without immunofluorescent staining of the kidney have been described in patients affected by APECED. These auto-antibodies recognize cytochrome P4501A2 as major target that is not expressed in kidney tissue. Anti-LKM-1 and anti-mitochondrial antibodies (AMAs) can display similar staining patterns, thus accounting for their possible misinterpretation. However, liver and renal tubule (particularly distal ones) substrates, as well as gastric parietal cells, are more intensely stained by AMAs.

Anti-LC-1 can be found in patients with type 2 AIH in association or not with anti-LKM-1. Anti-LC-1 staining typically involves the hepatocyte cytoplasm, with the exception of the centrilobular area (Fig. 2F), and the enzyme formimino-transferase-cyclodeaminase is its molecular target. Anti-LC-1 antibodies have also been detected in HCV chronic infection. However, Rigopoulou et al. showed that anti-LC-1 and anti-soluble liver antigen (anti-SLA) auto-antibodies are not detected by conventional enzyme-linked immunosorbent assay (ELISA) in a large group of HBV and HCV chronically infected patients in the absence of anti-LKM-1 auto-antibodies, suggesting that these auto-antibodies should not be tested for routinely, with the exception of anti-LC-1 screening in HCV-positive patients with concomitant anti-LKM-1 positivity.

Auto-antibodies directed to SLA/liver-pancreas (LP) antigens have also been reported in AIH. First described separately as anti-SLA and anti-LP, they were subsequently shown to target the same antigen and were then called anti-SLA/LP antibodies. They can be detected by radioimmunoassay, immunoblot, and/or ELISA techniques, although not by immunofluorescence. Anti-SLA/LP positivity in the absence of any other serological marker of AIH has been proposed for the definition of a potential type 3 AIH. Patients with anti-SLA/LP-positive AIH usually have a more severe disease.

By means of screening analyses of cDNA expression libraries, UGA tRNA suppressor-associated antigenic protein (tRNP[ser]sec) has been proposed as molecular target of anti-SLA. Given that this target has been redefined as Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase, anti SLA/LP can be referred to as anti-SEPSECS. In 2007, Liaskos et al. first noticed the simultaneous reactivity of anti-SLA and anti-ribonucleoprotein (anti-Ro)/Sjögren’s syndrome A antigen in sera from Greek patients with type 1 AIH. Seropositivity for both auto-antibodies was not related to cross-reactivity and was shown to be prognostically important in that it was a marker of a more advanced disease. Antibodies to Ro52 alone and associated with anti-SLA were independently associated with a poor outcome in type 1 AIH. Conversely, in a more recent study, treatment response, relapse of the disease after treatment withdrawal, and clinical outcome were not associated with anti-SLA, anti-Ro52, or both reactivities.

A final mention should be made of the possible detection of ANCAs in AIH, as well as in PBC and inflammatory bowel diseases. Usually, they involve perinuclear ANCAs rather than cytoplasmic ANCAs. Because they react with peripheral nuclear membrane components, the definition of peripheral anti-nuclear neutrophil antibodies (pANNA) has been suggested. Although pANNA are unusual in
type 2 AIH, in the absence of additional auto-antibodies, they could indicate an AIH. The detection of several non-conventional auto-antibodies with undefined clinical significance has also been reported in AIH patients. Among them, antibodies against α-actinin, an ubiquitous cytoskeletal protein also involved in systemic lupus erythematosus, have been described in AIH, typically with a double reactivity against f-actin, thus identifying a subset of patients with more severe disease. Asialoglycoprotein receptor (ASGP-R) is a glycoprotein mainly expressed on hepatocyte cell membrane at the peripoortal areas (where interface hepatitis occurs). Antibodies to ASGP-R are common in type 1 AIH and can identify frequently relapsing patients after corticosteroid discontinuation. Although AMAs are the serological hallmark of PBC, they have been detected also in AIH, but they probably do not characterize a particular subgroup. However, further studies are needed to define whether the presence of AMAs indicates a collateral bile duct injury or an underlying autoimmune cholestatic liver disease.

VI. DIAGNOSIS AND CLASSIFICATION

In 1993, the IAIHG proposed the diagnostic criteria for AIH, which were then revised in 1999. These criteria include the evaluation of aminotransferases and serum IgG levels, the occurrence of auto-antibodies, and the histopathologic features of interface hepatitis. In addition, sex, viral markers, alcohol consumption, drug history, concomitant immune-mediated diseases, response to therapy, HLA, and the presence of additional auto-antibodies (i.e. anti-SLA/LP, α-actinin, ASGP-R, pANNA) were considered. More recently, the same group has proposed a simplified scoring system for clinical practice. The system is based on a single positivity of ANA/SMA/LKM-1/SLA auto-antibodies, IgG serum levels, liver histology, and absence of viral hepatitis.

Type 1 AIH is characterized by the presence of ANAs and/or SMAs, which are detected in approximately 90% of cases. Clinical and histopathological severity is variable, as well as age at onset. Treatment failure is uncommon, but relapse rates are variable, suggesting that maintenance therapy should be given. Type 2 AIH, accounting for approximately 10% of cases, is characterized by positivity for anti-LKM-1 and anti-LC-1 antibodies, with anti-LKM3 detection being rare. Typically, disease onset is in childhood or in young adulthood, with acute clinical features and more histopathological severity. Treatment failure is frequent, as are relapses after drug withdrawal, thus requiring long-term maintenance therapy.

Whether the presence of anti-SLA/LP and/or Ro52 antibody is a distinct clinical feature of type 3 AIH is still a matter of discussion. This condition resembles type 1 AIH with a more severe clinical picture. Table 3 summarizes the main distinctive features of each condition.

Clinical and laboratory findings that characterize other AILD can sometimes be observed in AIH patients, who are usually defined as having “variant forms.” However, standardized criteria for their classifications are lacking. Several definitions, such as AIH/PSC or PBC overlap and autoimmune cholangitis, are usually used to differentiate these situations from the classical AIH, PBC, and PSC. In 2011, the IAIHG published a position paper on overlap syndromes. On the basis of available diagnostic criteria and study population, 2–19% of patients with PBC and 7–14% of those with PSC may display AIH-overlapping clinical, biochemical, immunological, and histopathological features.

VII. TREATMENT

The majority of the therapeutic studies of AIH were published during the 1970s and the 1980s. They clearly suggested the necessity to treat patients with moderate and severe hepatitis, evaluated on the basis of the following criteria: (1) histologic demonstration of confluent necrosis; (2) AST more than 5× ULN; and (3) gamma-globulins more than 2× ULN. Therapy improves liver function, symptomatology, and prognosis and often results in complete remission and prevention of disease progression. However, Lamers et al. reviewed 11 randomized-controlled trials about induction and maintenance treatment of both naive and relapsed patients showing lower remission rates. Therefore, it can be argued that, despite their clear benefit, prednisolone...
ne and azathioprine are not the ideal drugs for AIH and further studies are required to identify more effective molecules.\textsuperscript{152}

Induction therapy includes prednisolone at a starting dose of 0.5–1 mg/kg/d (e.g., 60 mg/d for a 60 kg adult patient, which is slowly tapered to 30–10 mg/d over a period of 4–10 weeks).\textsuperscript{7} The addition of azathioprine (1–2 mg/kg/d) is an equally effective regimen compared with prednisolone alone, but it is useful to prevent or reduce steroid-related side effects.\textsuperscript{17,50}

According to the EASL-CPG, for AIH, 50 mg/d of azathioprine should be started 2 weeks after the initiation of steroid treatment and increased in relation to clinical response and toxicity until reaching a maintenance dose. It is known that azathioprine effects are mediated via conversion to 6-thioguanine and 6-methylmercaptopurine, the latter substance being controlled by thiopurine methyltransferase (TPMT). Attention has therefore been drawn to patients with TPMT deficiency. Although in approximately 25% of AIH patients, there can be a discrepancy between TPMT phenotype and/or genotype on one side and response to azathioprine on the other, the enzyme activities were shown to be significantly lower in patients intolerant of azathioprine compared with those achieving remission on azathioprine alone and those who tolerated azathioprine but still required corticosteroids.\textsuperscript{153} In a later study, however, advanced fibrosis rather than TPMT genotype or activity was found to predict azathioprine toxicity in AIH.\textsuperscript{154} According to the EASL-CPG, TPMT testing should be performed before starting azathioprine therapy; however, a close surveillance of all patients undergoing azathioprine therapy is mandatory because the toxic effects are more frequent in the absence of TPMT deficiency.\textsuperscript{7}

A retrospective study on 22 patients has shown that the use of 6-mercaptopurine may represent a valid alternative in patients with previous intolerance to azathioprine, but it is usually ineffective in non-responders.\textsuperscript{155}

Based on the observation that an early fall or normalization of transaminases is a favorable prognostic factor,\textsuperscript{156} an initial dose of prednisolone of 1 mg/kg of body weight combined with azathioprine at a dose of 1–1.5 mg/kg of body weight has been suggested. Within the next 3 months, prednisolone is tapered to a maintenance dose of 5–10 mg/d and then discontinued after 1 year of treatment in patients achieving a biochemical response; patients are maintained on azathioprine until histological remission is also achieved.\textsuperscript{157} It might also be advisable to start with steroids and subsequently introduce azathioprine to establish whether a drop in transaminase levels occurs, thus avoiding the risk to consider as

\begin{table}
\centering
\caption{Main distinctive features of different types of AIH}
\begin{tabular}{|c|c|c|}
\hline
 & Type-1 & Type-2 & Type-3 \\
\hline
Auto-antibodies & ANA, SMA, anti-SLA/LP & Anti-LKM-1, anti-LC-1, anti-LKM3 (rarely) & Anti-SLA/LP Ro-52 antibody \\
\hline
Age at onset & Any age & Prevalently childhood and young adulthood & Similar to type-1 AIH \\
\hline
Clinical severity & Broad range & Generally severe & Possibly more severe \\
\hline
Histopathological features at onset & Broad range & Generally advanced & Similar to type-1 AIH \\
\hline
Treatment failure & Infrequent & Frequent & Similar to type-1 AIH \\
\hline
Relapse after therapy discontinuation & Variable & Common & Similar to type-1 AIH \\
\hline
Long-term maintenance therapy & Variable & Common & Similar to type-1 AIH \\
\hline
\end{tabular}
\end{table}

Definite AIH: score ≥7; probable AIH: score ≥6.

*Addition of points achieved for all auto-antibodies cannot exceed a maximum of 2 points.
non-responders patients with azathioprine-induced hepatotoxicity, especially patients with advanced liver disease. For a better evaluation of these conditions, long-term follow-up is required.\(^{158}\)

The use of budesonide (9 mg/d) instead of prednisolone has been considered in non-cirrhotic patients.\(^{159,160}\) The association of budesonide plus azathioprine has resulted in a remarkable reduction of side effects due to systemic steroid therapy.\(^{161}\) Little is known, however, about the best schedule for dose reduction or the long-term efficacy and safety of budesonide.

The obvious end point of induction therapy should be complete clinical, biochemical, and histological remission, a comprehensive outcome that does not occur in the majority of cases. Biochemical remission is defined as normalization of IgG and transaminases and histological remission as normal histology or minimal hepatitis (histology activity index <4 or equivalent).\(^{7,8,107}\) Conversely, given that total lack of response is observed in few patients, they should undergo a critical reconsideration of diagnosis and/or adherence to treatment. Usually, in 80–90% of patients, a rapid decline of liver enzymes can be observed soon after the introduction of therapy.\(^{162}\) In non-responsive patients with acute liver failure and no improvement of Model for End-Stage Liver Disease (MELD) score and bilirubin,\(^{163,164}\) liver transplantation should be considered.

Treatment withdrawal remains a clinical challenge. According to currently available guidelines,\(^{7}\) therapy should be prolonged for at least 3 years and 2 years after complete normalization of transaminases and IgG levels, respectively. The failed achievement of these goals may be considered predictive of relapse, histological activity, risk of progression into cirrhosis, and eventually of poor outcome.\(^{165}\) A new liver biopsy may be advisable before deciding to discontinue therapy. Even so, the frequency of relapse is high (approximately 50–90%) and usually occurs within 12 months.\(^{161}\) Later relapses are also described, suggesting the opportunity of a long-term follow-up.\(^{166}\)

Maintenance therapy, based on the increase of azathioprine to 2 mg/kg/d and the progressive tapering of steroids until suspension, can also be considered.\(^{167}\) Steroid monotherapy at the lowest dose capable of maintaining transaminases within normal limits is an alternative option. The choice of therapy should be individualized according to the stage of liver disease and severity on presentation, tolerance to treatment, associated diseases, and additional risk factors.\(^{152}\)

Clinical and laboratory parameters should be monitored during the first month of therapy and thereafter every 2–3 months. In patients with ongoing maintenance treatment, lifelong monitoring (every 3–6 months) is recommended to assess the risk of recurrence after therapy withdrawal and to evaluate drug toxicity or drug-related pathological conditions (i.e., potential oncogenic risk of azathioprine or steroid-related bone and metabolic alterations).

The use of other drugs has been proposed in patients with intolerance or lack of response to conventional regimens.\(^{168}\) Mycophenolate mofetil (MMF; 1.5–2 g/d), a purine antagonist inhibiting both T- and B-cell proliferation, is an alternative, effective drug.\(^{169}\) Prednisolone plus MMF combination therapy showed 88% of complete response (29% with relapses) in a cohort of 59 treatment-naive AIH patients.\(^{170}\) Efficacy and safety of MMF as first-line therapy were also confirmed in a recent prospective study evaluating the long-term efficacy of MMF in a real-world setting, in which 71.6% of patients had complete responses and 78.2% maintained remission without prednisolone.\(^{171}\)

Additional proposed drugs include calcineurin inhibitors (tacrolimus and cyclosporine), methotrexate, cyclophosphamide, rituximab, and anti-TNF antibodies such as infliximab. Cyclosporine has largely been used in the pediatric population, with good efficacy and high response rates; in adults, although it has been used in a limited number of patients, a good biochemical response has been reported.\(^{173}\) Similar preliminary results have been achieved with tacrolimus, which appeared promising for non-responsive AIH.\(^{174}\) Efficacy and safety of tacrolimus at a median dosage of 2 mg/d have been reported in a long-term follow-up study on 19 patients with difficult-to-treat type 1 AIH.\(^{175}\) However, the use of tacrolimus and cyclosporine in a real world setting was more prevalent in tertiary,
transplantation-oriented referral centers. The anti-TNF infliximab, retrospectively evaluated as a possible rescue therapy in difficult-to-treat patients, has been associated with a high rate of infectious complications. It should also be mentioned that the occurrence of an immune-mediated liver disease resembling AIH has also been described after the administration of anti-TNF agents. Their use should therefore be evaluated carefully and monitored closely. In a small series of six patients, a significant biochemical improvement was reported after two infusions of 1000 mg rituximab 2 weeks apart. Obviously, further studies are warranted for all of these drugs.

Liver transplantation is the ultimate therapeutic option in patients with fulminant hepatitis or end-stage chronic liver disease. The indication for liver transplantation occurs in approximately 4–6% of adult patients with AIH. Recurrence of AIH occurs in approximately 30% of patients receiving transplantations, with a clinical behavior similar to the primary disease. De novo occurrence of AIH in patients who underwent liver transplantation for non-AILD has also been reported.

VIII. CONCLUSIONS

Exactly 60 years have elapsed since AIH, at that time named “lupoid hepatitis,” was first described and its immune-mediated pathogenesis was hypothesized. Starting from 1973, the combination of prednisone plus azathioprine was shown to be highly effective and is still considered the standard of care. At the time of this writing (February 2017), the search for “autoimmune hepatitis” on PubMed retrieved 9083 papers. Therefore, it seems safe to state that the disease has been and continues to be the object of intensive investigations that have significantly improved our knowledge of its clinical, immunological, and therapeutic features.

Nevertheless, the following major issues should be emphasized. First, despite the availability of internationally validated diagnostic criteria, the initial diagnosis of AIH may sometimes be difficult given that the insidious onset of the disease that may range from non-specific symptoms to end-stage liver disease. Second, a deeper insight into the pathogenetic mechanisms underlying the onset of AIH should hopefully lead to the identification of molecular targets for the development of new drugs. Third, a better definition of the duration of induction therapy and the decision to shift to maintenance therapy need to be established. Fourth, a tailored choice of the best alternative drugs that should be used whenever standard treatments result ineffective, the patient is intolerant, or relapse occurs is still lacking. Finally, the advantages and potential dangers of lifelong immunosuppression have not yet been established clearly. These issues require further studies and multicenter randomized clinical trials.

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