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Review article

Role of Inflammasomes in Liver Disease and Autoimmune Hepatitis vs. Infectious Hepatitis: An Extensive Review

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Abstract

Autoimmune hepatitis (AIH) is a chronic inflammatory condition characterized by periportal inflammation, increased immunoglobulins and autoantibodies, and a significant response to immunosuppression. In genetically predisposed people, an environmental contaminant is thought to induce an immune-mediated attack against liver antigens. A wide range of clinical manifestations, from chronic indolent illness to fulminant hepatic failure, can be detected, and the diagnosis necessitates the exclusion of other causes of liver disease. Corticosteroid therapy must be started early and tailored to the person. The variety of clinical symptoms, uncertainty regarding the natural history, developing notions about therapeutic end targets, and the existence of many alternative immunosuppressive drugs can confound therapeutic decisions. The ultimate aim of the desired therapy is to achieve normal liver tests and tissue; however, this must be balanced against the danger of side effects. Early liver transplantation may be beneficial for decompensated patients. When therapy is started quickly and aggressively, the long-term prognosis is excellent. Our article addresses AIH and provides a thorough overview of its clinical presentation, risk factors, immunopathogenesis, modern diagnostic criteria, recent advancements in therapy, a brief discussion of AIH during pregnancy, and long-term effects on cirrhosis and hepatocellular carcinoma in patients with AIH.

Keywords: ***Autoimmune hepatitis; Infective hepatitis; Circulating autoantibodies; Hypergammaglobulinemia***

Core Tip

Autoimmune hepatitis (AIH) is characterized by autoantibodies, hypergammaglobulinemia, necrotic inflammatory changes in the liver, and a marked response to immunosuppressive treatment. Fundamental mechanisms of AIH have not yet been identified, and its clinical manifestations vary. Diagnosis necessitates the exclusion of other causes of liver disease. Therapy must achieve normal liver tests and tissue without side effects. This review of AIH provides a thorough overview of the clinical presentation, risk factors, immunopathogenesis, modern diagnostic criteria, recent advancements in therapy, a brief discussion of AIH during pregnancy, and long-term effects on cirrhosis and hepatocellular carcinoma in patients with AIH.

Introduction

Autoimmune hepatitis (AIH) is an idiopathic chronic inflammatory disease characterized by the presence of circulating autoantibodies, hypergammaglobulinemia, necrotic inflammatory changes in the liver tissue, and a remarkable response to immunosuppressive therapy. It was described in 1942 by Amberg [1] and in 1950 by Leber [2]. AIH is clinically characterized by hypergammaglobulinemia, high serum antinuclear antibody (ANA) titers, histological portal inflammatory cell infiltration, and macular necrosis, and defects in inhibitory T-cell-like asialoglycoprotein receptor or human lymphocyte antigen (HLA) are known genetic factors that contribute to AIH. Nevertheless, its fundamental mechanisms and triggers, which are currently the object of research, are yet to be identified [3]. Lately, inflammatory cytokines, which have been identified as major actors in the pathophysiology of AIH, have been the object of ongoing research. Interleukin (IL)-17, for instance, which has been demonstrated to induce hepatic inflammation and fibrosis, is secreted by immune cells that infiltrate and damage the liver and induces autoimmune liver disorders [4]. Acute hepatitis-causing viruses such as the hepatitis A virus (HAV), hepatitis B virus (HBV), and Epstein-Barr virus have been linked to some cases of AIH [5].

According to seropositivity, there are two different types of AIH: type 1 is defined by antibodies to smooth muscle antibodies or ANAs, and type 2 is defined by antibodies to liver-kidney microsome antibodies or liver cytosol antibodies. Although the true prevalence of AIH is unknown, women are more frequently affected than men (female:male = 3.6:1) [6,7]. A genetic predisposition, failure of immunoregulatory mechanisms, and environmental stimuli that cause an immune attack on the liver autoantigen that results in a progressive necroinflammatory and fibrotic process in the liver have all been proposed as potential mechanisms [7]. Toxins, viral infections, immune-suppressing medications, liver transplantation, or co-occurrence with other autoimmune illnesses are some of the described triggers [8]. To assist in the diagnosis of AIH, the International AIH Group (IAIHG) decided on a diagnostic score system [9]. The scoring system, which had 30 scoring elements and 13 separate criteria, was found to be too complicated to use in clinical settings. As a result, in 2008, the IAIHG created a streamlined scoring method that uses only four criteria: hypergammaglobulinemia, a rise in immunoglobulin G (IgG) concentration, the absence of viral indicators, the presence of histological characteristics typical of AIH, and the presence of particular autoantibodies [10,11]. The initial signs of liver disease include increments in serum aminotransferase (AST) levels, which are typically increased in AIH and during regular clinical testing. Nevertheless, aminotransferases have not been taken into account in the simplified scoring system because they are markers of hepatocyte damage that are high in many distinct types of liver disease. The existence of certain autoantibodies to liver autoantigens serves as one of the primary diagnostic criteria for AIH and its subtypes [12]. In general, AIH type 1 (AIH1) is characterized by the presence of antinuclear (ANA) and/or anti-smooth muscle (SMA) autoantibodies, whereas AIH type 2 (AIH2) is characterized by type 1 liver/kidney microsomal autoantibodies (LKM1) [8,13,14]. In terms of clinical presentation and disease progression, patients with AIH type 1 differ from those with AIH type 2 [15]. Because there have been numerous recent reviews that concentrate on autoantibodies in patients with AIH, we will only briefly touch on the most crucial points. ANA is present in individuals with primary biliary cirrhosis (PBC), systemic sclerosis (SSc), drug-induced hepatitis, chronic hepatitis B or C, and nonalcoholic fatty liver disease, despite being frequently used to categorize patients with AIH1 [16].

Classification and Diagnosis of AIH

There are now four different categories for AIH. Type 1 AIH is more prevalent in adults (aged 45-70 years), and it can affect younger persons (10-20 years old). It is distinguished by a moderate course and the predominance of antibodies (ANA and/or ASMA), antihypergammaglobulinemia, and F-actin. Type 2 AIH typically affects young children and adults (however, it is most prevalent in children aged 2-14 years). It progresses quickly and is frequently accompanied by anti-LKM antibodies, which include the anti-LKM1, anti-LKM2, and anti-LKM3 varieties. Anti-LKM1 is the most prevalent of these three types of antibodies (anti-LKM1, anti-LKM2, and anti-LKM3) for type 2 AIH. Additionally, in the event of hepatitis C virus (HCV) infection, their existence can be seen. Anti-SLA/LP antibodies, as well as LC-1, are additional antibodies that are frequently seen in type 2 AIH (anti-liver cytosol antibodies). Type 3 AIH has a clinical trajectory similar to that of type 1 AIH. Anti-SLA/LP antibodies are present, which defines it. Ninety percent of cases are adult women between the ages of 30 and 50 years [17].

The International AIH Group has created codified criteria for the diagnosis of AIH [18]. The International Autoimmune Hepatitis Group created a scoring system for the diagnosis of AIH in 1999, which was updated in 2010 (**Table 1**). The requirements include interphase hepatitis, compatible liver histology, high blood IgG, liver autoantibodies, elevated serum transaminases, and a negative viral hepatitis serology. At parenchymal-connective tissue junctions (interphases) around the portal tracts, interphase hepatitis is characterized by lymphocytic infiltration with or without plasma cells and concomitant hepatocyte cell death (piecemeal necrosis). At any age, individuals with increased liver enzyme levels and/or unexplained cirrhosis should have AIH on their differential diagnosis list.

Given the lack of a clear diagnostic marker and the inconsistent clinical and laboratory data, the diagnosis might be difficult to make. Interface hepatitis, the absence of alternative reasons for the lesions (such as viral hepatitis or drug-induced hepatitis), and evidence of autoimmunity are characteristics of AIH (autoimmune antibodies or concomitant autoimmune diseases) [19]. In Table 2, the diversification of various forms of AIH is shown in relation to the prevalence of specific autoantibodies.

Table 1: Simplified International Autoimmune Hepatitis Group score system

Autoantibodies		
ANA or SMA	***≥1:40***	***+1***
ANA or SMA	***≥1:80***	***+2***
Antibodies to Liver Kidney microsome type 1	***≥1:40***	***+2***
Antibodies to soluble liver antigen	***Positive***	***+2***
Absent autoantibodies	***None***	***0***
Immunoglobulin Level		
Immunoglobulin G	***> ULN***	***+1***
	> 1.1 ULN	***+2***
	Normal	***0***
Histological Findings		
Morphological Features of AIH	***Compatible***	***+1***
	Typical	***+2***
	Incompatible	***0***
Viral Disease		
Absence of Viral Hepatitis	***No Viral Markers***	***+2***
	Viral Markers Present	***0***
Pretreatment Aggregate Score	***Definite Diagnosis***	***≥ 7***
	Probable Diagnosis	***6***

Table 2: Categorization of autoimmune hepatitis (AIH) based on the presence of autoantibodies

AIH types	Antibody	Prevalence
1	Anti-SLA/LP	10%-30%

	ASMA	40%-90%
	ANA	5%-70%
2	Anti-SLA/LP	10%-30%
	Anti-LKM-1	2%-4%
3	Anti-LC1	1%-2%
Cryptogenic hepatitis	Absence of antibodies	

Laboratory Findings

Although aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are frequently elevated in the laboratory, their levels are typically 500 U/L; however, on rare occasions, they can range between 500 U/L and 1000 U/L. It may be necessary to rule out drug-induced illness, PBC, primary sclerosing cholangitis, extrahepatic biliary blockage, and excessive conjugated bilirubin and alkaline phosphatase in some cases (PSC). Alkaline phosphatase levels rarely rise above four times the normal levels and typically remain approximately two times the normal levels. Hypergammaglobulinemia, with a selective increase in IgG (1.2-3.0 times higher than the upper level of normal), is another distinctive laboratory sign of AIH [20]. Although HLA typing has not been approved as a diagnostic or prognostic tool, it should be mentioned.

Autoantibodies

As previously stated, AIH is a pathogenetically inhomogeneous entity that develops when immunocompromised cells lose their tolerance to autogenously hepatic tissue components [21]. The presence and pattern of autoantibodies play a crucial role in the diagnosis, differential diagnosis with other immune-mediated hepatobiliary disorders, and type 1 or type 2 variant identification [22]. Currently, serum biomarkers such as AST/ALT, IgG, ANA, SMA, 6-TG (thioguanine), and LKM1 (AIH2) are used for the diagnosis of AIH. However, these biomarkers have limitations in terms of sensitivity, specificity, and predictive value. Hence, there is a need to explore new biomarkers for the early diagnosis, disease monitoring, and personalized treatment of AIH. Recent studies have identified several candidate biomarkers for AIH. For instance, serum levels of TGF-beta1, TNF-alpha, B cell activating factor (BAFF), ADA, and Treg cells have been proposed as potential biomarkers for AIH [23]. PD1 and CTLA4 antibodies have also been studied as possible biomarkers for predicting the response to therapy in patients with AIH patients. IL22 mRNA has been found to be elevated in the liver tissue of patients with AIH, suggesting its potential as a diagnostic biomarker. Additionally, anti-AGPR Abs, MIF, and DNAse 1 have been identified as promising biomarkers for AIH. Vitamin D has also been proposed as a potential biomarker for AIH. Vitamin D, which is known to have immunomodulatory effects, has been found to play a role in the pathogenesis of several autoimmune diseases, including AIH. Studies have shown that vitamin D deficiency is prevalent in patients with AIH and is associated with disease activity and severity [24]. Vitamin D supplementation has been found to improve liver function tests and reduce disease activity in AIH patients, which is discussed separately.

Ferritin is another biomarker that has been studied in the context of AIH. Ferritin is an iron-storage protein that has been found to be elevated in several liver diseases, including AIH. Elevated serum ferritin levels have been associated with liver inflammation and fibrosis in patients with AIH patients.

Antibodies that are specific for antigens found in cell nuclei are referred to as ANAs. In the nucleus, antigens are found on the RNA and DNA, histones and nonhistones, and determinants, which are composed of both nucleic acid and protein components (e.g., the ribonucleoprotein antigen, antigen U-RNP). For each of these several nuclear components, distinct ANAs have specificity. In systemic lupus erythematosus, ANA is typically directed against double-stranded DNA; however, the target epitope appears to be different in the two conditions [23]. Immunofluorescence (a traditional method) or the more contemporary enzyme-linked immunosorbent test technology can both identify ANA in a patient's serum. In AIH1, they are frequently positive.

AIH1 commonly contains ASMAs, which have a preference for actin and other cytoskeleton elements [24]. Approximately 60% of the patients have it. The smooth muscle autoantibody has been found to react with F-actin microfilaments in skeletal muscle, cardiac muscle, and nonmuscle cells such as gastric parietal cells and brain synapses because of its reactivity with smooth muscle [25]. Using platelet actin as an immunoabsorbent, Gabbiani et al [26] made the first demonstration of specificity for actin. The immunofluorescence (IF) labeling of the gastric muscularis externa, muscularis mucosa, and smooth muscle fibers that stretch from the muscularis mucosa into the lamina propria enables the identification of the smooth muscle autoantibody in normal diagnostic laboratories. The extra distinctive pattern of the IF staining of contractile fibrils around the renal tubules serves as a marker for the F-actin-specific smooth muscle autoantibody, as shown in Figure 1.

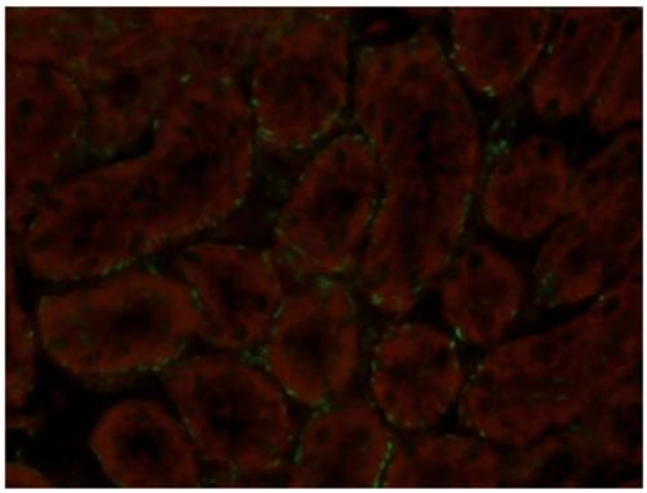

Figure 1. SMA-T smooth muscle antibody that is specific for F-actin attaches to renal tubules in a "picket-fence" pattern by immune-fluorescence contractile fibrils (Courtesy of Toh BH [27]).

Type 1 autoimmune hepatitis can be diagnosed using the F-actin reactive smooth muscle autoantibody, antinuclear autoantibody, and autoantibody to SLA/LP; conversely, type 2 autoimmune hepatitis can be identified by the LKM-1 and LC-1 autoantibodies. An overview of the diagnostic autoantibodies in autoimmune hepatitis is given in Table 3.

Table 3: Diagnostic autoantibodies in autoimmune hepatitis

Type 1 autoimmune hepatitis	F-actin reactive smooth muscle autoantibody
	Antinuclear autoantibody
	SLA/LP autoantibody
Type 2 autoimmune hepatitis	LKM-1 autoantibody
	LC-1 autoantibody

Anti-smooth muscle antibodies (ASMA), antinuclear antibodies (ANA), liver/kidney microsome antibodies (anti-LKM), anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP), anti-liver cytosol antibodies (anti-LC1).

Epidemiology

The majority of the accessible data are on AIH1. AIH1, which accounts for approximately 80% of AIH cases, is found worldwide and has a strong female predominance (75% of those affected are females) [28]. For a very long time, it was believed that it mostly affected young and middle-aged women, peaking in youth and then again around the age of 40 [22]. However, it is now known that older persons can also be impacted and that the disease can begin to show symptoms even at an advanced age (20% of patients get sick after the age of 60) [29]. In different geographical areas, AIH has a different incidence and different characteristics. AIH, a chronic condition, affects 10-17 people per 100,000 in Europe, 17 per 100,000 in Norway, and 31 per 100,000 in the US. In Japan, this sickness is far less common. Similar data were found in a Spanish study that reported an annual incidence of 0.8 cases per 100,000 people and a prevalence of 11.6 cases per 100,000 people, which translates to an estimated point prevalence of 10-15 cases per 100,000 people [30]. Around the world, the prevalence of the disease has tended to rise [31,32].

Etiopathogenesis

Etiology

The etiology of AIH is not entirely understood. Genetic, environmental, toxic, and infectious variables, such as HAV, HCV, hepatitis E virus (HEV), measles morbilli virus, Epstein-Barr virus (EBV), and herpes simplex virus, as well as medicines, may play the most essential role [33].

Because infections with pathogens frequently result in the onset of both innate and adaptive immune responses, pathogens have been linked to the etiology of numerous autoimmune disorders [34]. Depending on the type of pathogen, the subsequent immune response elicits either more of a type 2 phenotype (allergic), which is necessary for the elimination of extracellular parasites such as helminths, or more of a type 1 phenotype (aggressive and cytotoxic), which is required for the elimination of intracellular pathogens such as viruses [34]. Because most autoimmune disorders are characterized by an intense type 1 immune response, viruses are the main suspects in the development and/or spread of an autoimmune process. Although connections with a wide range of pathogens have been identified for almost all autoimmune illnesses, concrete evidence that these infections are responsible for the start and/or spread of autoimmune damaging processes is sometimes lacking. Finding concrete evidence might be challenging because of several factors. First, not all patients have a history of infection with a certain pathogen, and not everyone exposed to a certain pathogen develops the autoimmune illness that goes with it. Second, even though some patients may have previously come into contact with a specific pathogen, at the time of disease diagnosis, there are no signs of infection with a pathogen because the pathogen has been completely eradicated and there is no detectable antibody titer. These nonchronic infections with such pathogens are referred to as “hit-and-run” incidents. Third, a breakdown of the barriers preventing commensal microorganisms from escaping the stomach may also cause bystander inflammation. According to a recent study, certain gut pathobionts may be responsible for the autoimmune reactions in peripheral organs [34]. The translocation of the gut pathobiont, Enterococcus gallinarum, to the liver induced cytokines, autoantigens, endogenous retrovirus proteins, and other autoimmune-promoting factors in transgenic mice predisposed to develop systemic lupus erythematosus (SLE) in a bystander fashion [35]. Fourth, the onset of an autoimmune illness may involve infections by more than one pathogen. As a result, some viruses may start autoimmune processes that do not progress to clinical disease, whereas other pathogens may just speed up an autodestructive process rather than start one from scratch. Fifth, tropism and pathogen strain are other crucial variables. Although infection of the target organ may not always be necessary for the onset of an autoimmune illness unique to that organ, the resulting local inflammation may be necessary for the eventual development of an autoimmune disease. Finally, infections with some pathogens, especially helminths, may guard against negative immune reactions rather than trigger or intensify them [36].

Numerous strategies have been proposed as to how infections could start or speed up autoimmune reactions. First, infections with intracellular pathogens, such as viruses, frequently result in direct cell damage and generate an upregulation of MHC molecules on the surface of these infected cells and on trained antigen-presenting cells (APC), which serve as scavengers of the injured infected cells. Increased antigen presentation of peptides originating from both the invading pathogens and the host cells coincides with upregulated MHC expression [37]. The activation of polyclonal B or T cells is the first pathway.

The truth of the involvement of these processes is difficult to discern. The fact that autoantigen-driven selection is not a primary process in this context would indicate that there should be a paucity of somatic mutations in the autoantibody gene segment corresponding to complementarity-determining regions in autoreactive T cells. Except for some cases of SLE, this is rarely the case [38,39]. However, some autoimmune conditions can probably be explained by the significant B- and T-cell activation that is seen in some diseases, particularly viral and parasitic conditions.

Antigen mimicry is the second mechanism. A variety of bacterial or viral protein sequences have been found to have similarities with autoantigen sequences.

Pathogenesis

Several potential routes leading to an autoimmune attack on the liver have been proposed (**Figure 2**). Because the antigen targeted by anti-LKM1 has been identified as cytochrome P4502D6, most gains in research on AIH pathogenesis have happened in AIH2, the typically juvenile version of the disease (CYP2D6 [40]), allowing the identification of both CD4 and CD8 T lymphocytes that target this cytochrome CD4 T cells from AIH2 patients with the predisposing HLA allele DRB1*0701 recognizing seven CYP2D6 sites, five of which are also recognized by CD8 T cells [40]. The amount of interferon-producing effector T cells correlates with the biochemical evidence of liver injury [42]. The process of autoantigen recognition is closely controlled by regulatory mechanisms in the normal state. The failure of these systems causes the autoimmune onslaught to begin and continue [43,44]. In AIH, immunoregulatory systems have been consistently identified as being impaired. These patients exhibit a decrease in the number of CD4+CD127− T cells that express the IL-2 receptor (IL-2R) alpha chain (CD25)-regulatory T cells (Tregs). In health, these cells account for 5%-10% of the total CD4 T lymphocyte peripheral population and regulate innate and adaptive immune responses by inhibiting autoreactive T-cell proliferation and effector function. Treg abnormalities in AIH are more visible at diagnosis than during drug-induced remission; however, Treg counts do not reach healthy levels even during remission [45]. The percentage of Tregs has been demonstrated to correlate inversely with disease severity biomarkers, implying that a decrease in the Treg percentage favors autoimmune liver disease. Several investigations have found that Tregs from patients with AIH at diagnosis are less capable of controlling the proliferation of CD4 and CD8 effector cells than Tregs obtained from AIH patients in remission or from healthy subjects. Furthermore, effector CD4 T cells isolated from patients with AIH patients are less responsive to Treg regulation. This deficiency is associated with the decreased expression of the inhibitory receptors, T-cell-immunoglobulin and mucin-domain-containing molecule-3 (Tim-3), which promotes effector cell death upon the ligation of galectin-9 produced by Tregs [46].

In genetically susceptible individuals, liver damage could be orchestrated by CD4-positive T lymphocytes recognizing a self-antigenic peptide recognized by an HLA class II molecule and presented to uncommitted T helper (Th0) cells by professional APCs, with the costimulation of the ligand-ligand interaction (CD28 on Th0 and CD80 on APC). Activated Th0 cells develop into functional phenotypes based on the cytokine milieu and the nature of the antigen, triggering a cascade of immunological reactions. Type 1 T helper (Th1) cells mostly emit IL-2 and interferon (IFN) in the presence of macrophage-produced interleukin (IL)-12.

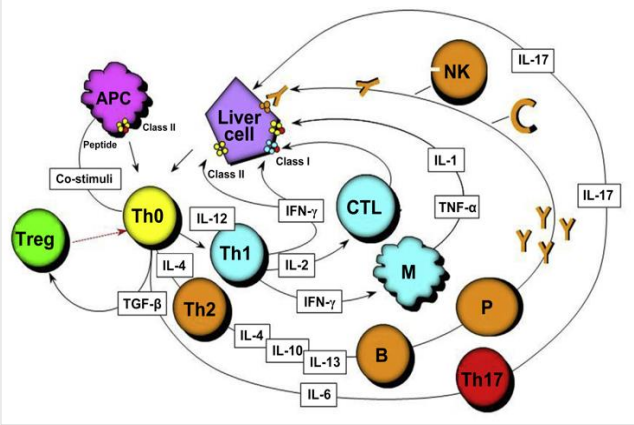

Figure 2. Proposed pathogenesis of autoimmune hepatitis (Courtesy of R Liberal [47])

Genetic Associations

Genetic relationships vary in studied populations, and AIH is a complicated polygenic disease with multiple genetic and environmental risk factors. The HLA genes on chromosome 6 are the relationship with AIH that is most frequently mentioned. A summary of HLA correlations by ethnicity is shown in Table 4. The age of presentation, disease severity, and therapeutic response may all be correlated with HLA. It is unclear exactly how the HLA genes contribute to the disease risk; however, it is most likely because of their function in the presentation of autoantigenic peptides and the selection of autoreactive T cells. The amino acids, LLEQKR or LLEQRR, at positions 67-72 of class II HLA are known as a "common motif" among several susceptibility alleles, including HLA DR-1-0301, DR-1-0401, DR-1-0404, and DR-1-0405, whereas the resistance allele, DR-1-1501, encodes ILEQAR. Conversely, HLA DR-1-1501, which is associated with protection from AIH, encodes for the ILEQAR motif [48].

It is hypothesized that changing the polarity and charge of the peptide-binding groove of the major histocompatibility complex at position 71 will affect how autoantigenic peptides are presented. However, these relationships are not universal, and there are important regional variations. For instance, in Japan, DR2 (DRB11501) is a weak susceptibility allele rather than a resistance gene [48], and in children from South America, DRB11301 is a strong susceptibility allele [49].

Table 4: HLA associations in autoimmune hepatitis

HLA association (Reference)	Ethnicity/Comments	AIH Type	Number of patients studied	Patients	Controls
HLA-DRB1*0401	(i) European and North American Increases susceptibility to AIH Type I in Caucasians (ii) HLA-DR3 associated with younger age at presentation, diminished response to therapy and more frequent liver failure requiring liver transplantation as compared to HLA-DR4	I	119	45%	23%
HLA-DRB3*0101 [15]	European and North American	I	119	58%	25%
HLA-DRB1*0404 [16]	Mexican	I	30	36.7%	7.4%
HLA-DRB1*0405 [17]	Japanese	_	49	67.3%	29.6%
HLA-DRB1*07 [18]	Brazil	II	28	68%	20%
HLA-B14 [19]	Germany	II	19	26%	4%

Pathogens and Autoimmune Hepatitis

As previously stated, there is a significant distinction between the observed relationship between pathogen infections with the onset of autoimmune diseases and real proof of pathogens' involvement in disease pathogenesis. However, because of the highlighted challenges associated with obtaining adequate data, such connections are frequently the only indication of the influence of environmental triggering variables such as infections.

Viral Hepatitis

Surely, viral hepatitis is the first suspect that comes to mind when thinking about infection as cause of AIH. Hepatotropic microorganisms, such as hepatitis viruses, induce direct liver damage and local inflammation. As a result, it is not surprising that hepatitis A, B, and C viruses have been linked to AIH. A link between hepatitis A infection and autoimmune hepatitis was discovered in a group of 58 patients, all of them were first-degree relatives of patients with AIH in the early 1990s. Three relatives tested positive for subclinical hepatitis A, however, two among three of them developed autoimmune hepatitis within five months [50]. Viral infections are capable of inducing immune dysregulation, which results in the loss of self-tolerance and subsequent autoimmune responses. These infections can also cause molecular mimicry and epitope spreading, further exacerbating the autoimmune response. The generation of immune complexes between HBV antigens and antibodies can also contribute to tissue damage and loss of tolerance. HBV-induced apoptosis and tissue damage can result in the exposure of intracellular antigens to the immune system, further contributing to the breakdown of immune tolerance. Toll-like receptors (TLRs) on innate immune cells are capable of recognizing microbial components and triggering an immune response. However, excessive TLR activation can lead to the breakdown of immune tolerance and the development of autoimmune diseases. Despite testing negative for the most prevalent autoantibodies, namely, ANA and LKM1, the two patients developed anti-LSP antibodies, which are present in up to 88% of AIH patients and are frequently observed to be transiently present in patients with acute hepatitis A [51]. The most common pathogen-AIH relationship has been identified for HCV. Typical autoantibodies detected in patients with AIH1 have also been found in patients with chronic hepatitis C. SMA and ANA, in particular, have been identified in up to 66% and 41%, respectively, of patients with HCV [52]. Moreover, Furthermore, both SMA and ANA have been seen in the sera of patients infected with HBV or the hepatitis D virus [53]. It

is important to emphasize that unlike well-defined autoantibodies such as LKM1, which detect CYP2D6, SMA, and ANA describe a heterologous antibody reactivity to smooth muscle actin and nuclear antigens, respectively. Thus, a comprehensive examination of the histological patterns of SMA indicated that AIH1 SMA reacts to arterial vessels as well as renal glomeruli and tubules, whereas SMA from HCV-infected patients mostly stains arterial vessels [54]. Furthermore, the nuclear staining of ANA appears uniform for ANA from patients with AIH1 and speckled for ANA from patients infected with HCV [55]. These data suggest that the existence of SMA and ANA in hepatitis virus-infected patients does not provide evidence that these viruses are involved in the pathogenesis of AIH. This is especially true for ANA, which is reactive to many different nuclear antigens, such as nuclear body-associated protein sp100 or nuclear pore membrane protein gp120 (both of which are present in the majority of PBC patients), DNA, centromeres, histones, snRNPs, and cyclin A, and is found in patients with AIH, PBC, and chronic hepatitis B or C infection, as well as drug-induced hepatitis [56].

Epstein-Barr virus

EBV is a ubiquitous virus that infects almost everyone during their lifetime and stays dormant in the cells of hosts for the rest of their lives. However, in some cases, the virus can be reactivated and cause a range of conditions, including autoimmune diseases. Recent studies have shown that EBV can modify the host's immune response and induce the production of autoantibodies, leading to the breakdown of self-tolerance and the development of autoimmune diseases. The global prevalence of autoimmune diseases reflects the ubiquitousness of the EBV pathogen. Patients with autoimmune diseases often have higher levels of EBV antibodies and viral DNA in their blood compared to healthy individuals. Moreover, EBV infection can trigger the activation of autoreactive T cells and B cells, leading to antibody production and the development of autoimmune diseases.

The association of EBV infection is well established with various autoimmune diseases, such as autoimmune thyroiditis (Grave's disease and Hashimoto's disease), multiple sclerosis (MS), Sjögren's syndrome, SLE, rheumatoid arthritis (RA), and autoimmune hepatitis [57]. A 2-year-old girl who recently contracted EBV developed typical symptoms of AIH. This is just one of many case reports that describe the development of AIH after EBV infection [58]. Despite the near timing of the EBV infection and the onset of AIH, there was no evidence to support a causal link between the two occurrences. Finding evidence is particularly challenging for EBV because the virus is thought to be present in up to 98% of people worldwide, and most people continue to be infected with it [59]. Vento et al [60] conducted a significant prospective investigation with a cohort of relatives of 13 AIH patients and found that two among seven females with infectious mononucleosis secondary to EBV also developed autoimmune hepatitis type 1 in a precise tentative relationship [60]. The intriguing aspect of this observation is that prior to EBV infection, both women had elevated titers of LSP antibodies against the asialoglycoprotein receptor (ASGPR). A deficiency in a population of suppressor/regulatory T cells that regulate the immunological response to ASGPR 101 led to this elevated titer. Thus, EBV infection may have sped up (rather than started autoimmunity in the liver from scratch), leading to clinically evident AIH. More evidence that autoimmune hepatitis and Epstein Barr virus relationship has been found in several other case studies [61-65]. In most of these cases, individuals who originally had signs of an acute EBV infection such as severe sore throat, fatigue, fever, lymphadenopathy, pharyngitis and swollen tonsils quickly progressed to AIH. Another instance in which the order of events is unusual: A 22-year-old lady with AIH who was diagnosed six years earlier was discovered to have a persistent active EBV infection by Chiba et al [66].

HBV and autoimmune hepatitis

AIH is distinguished by fluctuating serum ALT levels, significant hypergammaglobulinemia, and circulating organ-specific and non-organ-specific autoantibodies. Although it is uncommon and with female predominance, a hereditary susceptibility has been proposed [11,58]. Its prevalence ranges between 0.01% and 0.02%. AIH is distinguished by a significant increase in serum IgG titers. Recurrent necroinflammatory events inside the liver lobules and at contact with the portal tracts characterize the natural course, eventually leading to cirrhosis and, possibly, liver failure. Type 1 and type 2 AIH are distinguished by high titers of autoantibodies to nuclei (ANA) that are reactive to chromatin and occasionally dsDNA and/or antibodies to smooth muscle substrates (SMA) that are reactive to F-actin microfilaments. Type 2 is uncommon (20 times less common than type 1); however, it is more common in younger people with typical type 1 antibodies against liver/kidney microsomes (LKM1) directed against the cytochrome P450 isoform, 2D6 [67]. If a trigger is needed to initiate a chain of events that leads to AIH type 1 in a predisposed individual, viruses are among the most plausible choices. Two case reports have connected hepatitis B virus infection to AIH type 1: the first included a young woman who had recovered from acute HBV infection.

The second, which occurred in a chronic HBV carrier, was coincident with the appearance of a mutant, HBeAg-negative virus and was directly tied to viral multiplication as the disease resolved after HBV replication was inhibited [67]. Murakami et al [68] authored the case report of a 43-year-old Japanese lady diagnosed with AIH ten years after HBV infection. The diagnosis was based on the fact that she remained an asymptomatic HBV carrier with a normal liver function between testing positive for HBsAg and the onset of AIH. This woman was hospitalized ten years later, and an increased serum ALT level was discovered. Her HLA type was also shown to be DR4, which is strongly connected with AIH in Japanese people.

Management Of AIH

Indications for treatment

As previously stated, severe untreated AIH has a poor prognosis [69]. Adequate treatment can significantly improve the prognosis of the disease. Absolute indications for AIH treatment have been established based on the criteria associated with a poor prognosis (**Table 5**). A few randomized, controlled trials have shown that patients with AST levels of at least 10 ULN or greater than fivefold ULN in combination with a serum gamma-globulin level greater than twofold ULN had a significant mortality rate if left untreated [69-71]. At presentation, histological evidence of bridging necrosis or multilobular necrosis appears after cirrhosis in 82% of untreated patients and is associated with a 45% 5-year mortality [72,73].

Symptomatic patients with serum AST and/or gamma-globulin levels less than the absolute criteria, as well as interface hepatitis, may be indicated for immunosuppressive treatment on an individual basis, with the potential risks of therapy considered. Patients with little or no disease should not be treated; rather, they should be constantly monitored.

Immunosuppressive therapy should not be started in patients who have substantial pre-existing comorbidities (vertebral compression, psychosis, brittle diabetes, or uncontrolled hypertension) or a history of steroid resistance. Azathioprine therapy should not be commenced in patients who have severe pretreatment cytopenia (leukocyte count: ≤2.5 x 109/L or platelet count: ≤50 x 109/L) or a known thiopurine methyltransferase activity deficiency [22].

Table 5: Indications for the treatment of autoimmune hepatitis

	Absolute	Relative	None
Clinical	Incapacitating symptoms	Symptoms (fatigue, arthralgia, jaundice, abdominal pain)	Asymptomatic
Laboratory	AST≥tenfold ULN, AST≥fivefold ULN and HG≥twofold ULN	AST or HG less than absolute criteria	Normal or near normal AST and γ globulins
Histology	Bridging necrosis or multiacinar necrosis on histology	Interface hepatitis	Inactive cirrhosis or mild portal hepatitis

Standard treatment

The usual treatment for AIH is based on the findings of randomized studies conducted in the 1970s, which showed that corticosteroid treatment improved survival. These trials also confirmed the poor prognosis of untreated symptomatic AIH, with the 5-year survival of untreated patients falling to 25% compared to 80% for those treated with corticosteroids [69,70]. Based on the Mayo Clinic experiment, the American Association for the Study of Liver Diseases practice guidelines [22] indicate either monotherapy with prednisone at a starting dose of 40-60 mg daily or a lower dose of prednisone (30 mg daily) combined with azathioprine (1-2 mg/kg body weight). The prednisone dose can be lowered by 10 mg per week to a maintenance dose of 20 mg. Further reductions to 10, 5, or 2.5 mg daily are possible [69]. The usage of the prednisone metabolite, prednisolone, which is more commonly used in Europe, is as beneficial because chronic liver diseases do not appear to affect its synthesis. A higher starting dose of prednisolone (1 mg/kg body weight) may elicit remission more quickly and may help in saving steroids in the long run [72,74]. Acne, facial rounding, striae, weight gain, hirsutism, and emotional instability are among the side effects of steroids. Long-term treatment should be accompanied by serious problems such as steroid-induced diabetes, osteopenia, aseptic bone necrosis, mental symptoms, hypertension, and cataract formation. After 24 months of medication, 80% of patients experienced side effects. The side effects of azathioprine include bone marrow suppression, nausea, vomiting, rash, cholestatic hepatitis, and pancreatitis. Testing for thiopurine methyltransferase activity does not predict cytopenia. The activity of this enzyme is determined only when there is pretreatment or intertreatment cytopenia or when greater than typical doses are required [27]. The standard therapy outcomes are remission, recurrence, or treatment failure. Complete remission is defined as the absence of clinical symptoms and the complete normalization of all inflammatory markers, including histology. After 24 months of treatment, it is achievable in 65%-75% of individuals. Because the histological resolution of inflammation takes 3-6 months longer than the biochemical response, the medication must be continued beyond the normalization of aminotransferase levels. A minimum of three years of continuous therapy is recommended [22]. Withdrawal tapering schemes should be conducted with extreme caution and only after a liver biopsy has revealed complete remission of inflammatory activity. In that situation, prednisone can be reduced over 4-6 weeks to see if sustained remission has been established. Although steroids are the drugs of choice for remission induction, azathioprine is the drug of choice for remission maintenance [75]. A relapse is defined as an increase in aminotransferase levels and the recurrence of clinical manifestations while on treatment, after steroid tapering, or after the complete discontinuation of therapy. It affects 50% of patients within six months of therapy discontinuation and 80% after three years of therapy discontinuation. When a relapse occurs, normal therapy must be restarted until remission is achieved. In patients who are unable to tolerate azathioprine, the treatment can be changed to 2 mg/kg daily of azathioprine or low-dose prednisolone. Withdrawal attempts can be considered in all patients with prolonged (12 months) inactive illness [76].

Treatment failure, which is defined as disease progression with standard therapy, affects approximately 10% of patients. The diagnosis of AIH should be carefully evaluated in these circumstances. Experimental regimens can be used. Figure 3 summarizes their criteria and subsequent interventions [77].

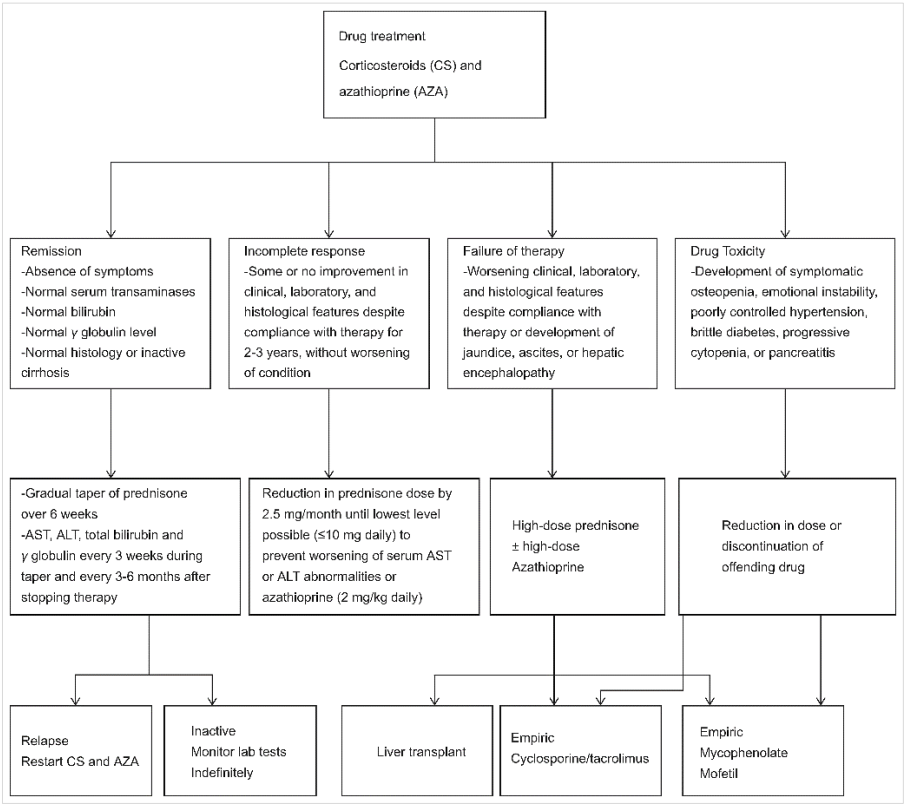

Figure 3. Endpoints of immunosuppressive treatment with the course of action in AIH (Courtesy of Makol et al [77]).

Alternative treatments

Budesonide is a synthetic steroid with approximately 90% first-pass metabolism in the liver, a feature that allows it to limit systemic side effects when compared to conventional steroids. The absolute bioavailability of this drug is less than sixfold reduced when compared to prednisone [78]. A combination of budesonide and azathioprine was tested in noncirrhotic individuals in major European research [79]. Budesonide was compared to prednisone 40 mg daily (reduced per protocol) (both arms plus azathioprine 1-2 mg/kg daily) at a dose of 3 mg three times daily (tapered to bid upon biochemical remission after two weeks based on clinical opinion). Remission was obtained in 60% of patients in the budesonide group but just 39% of patients in the prednisone group after six months. Budesonide had a significantly better profile of steroid-related adverse effects. It should be emphasized that the remission rate in the prednisone group is significantly lower than that observed with a greater initial dose of prednisone lowered based on the biochemical response. Furthermore, owing to the possibility of shunting, budesonide was not studied in cirrhosis [79]. However, the experiment suggests that budesonide is a viable alternative for people who are at risk of experiencing the adverse effects of steroids. Mycophenolate mofetil (MMF) appears to be a relatively good alternative for those who are intolerant to azathioprine [80,81]. However, there was no substantial improvement with MMF in another study conducted on individuals with AIH who had azathioprine failure or intolerance. There have been no controlled clinical trials testing MMF in either treatment-naive or treatment-experienced AIH patients. In recent prospective studies, the combination of MMF and prednisolone was compared with azathioprine as a first-line treatment for AIH. The biochemical response rates were outstanding, with 88% of the 59 patients obtaining complete remission within the first year of treatment. The use of MMF as the first-line treatment for patients with AIH has various disadvantages, including its high cost (approximately 15 times that of azathioprine) and teratogenicity.

Conclusion

It is obvious that infectious hepatitis and AIH are somehow connected when relevant information regarding the connection between HBV, HAV, HEV, HCV, and autoimmune diseases is taken into account. HBV, HCV, and HEV have been implicated in several pathways that cause certain autoimmune disorders. These include the production of immunological complexes between HBV antigens and antibodies, molecular mimicry between HBV antigens and self-proteins, and apoptosis/tissue destruction that exposes intracellular antigens [82-85]. With the exception of the instance where HBV has been demonstrated to cause PAN, all other data, to date, do not establish a causal link between HBV and the onset of autoimmune disorders. It is possible to infer that patients with autoimmune diseases are more likely to contract HBV. Some investigations have found autoantibodies after HBV infection, although these patients seldom develop an autoimmune illness as a result of the autoantibodies. It should be emphasized that an autoimmune disease may develop years before symptoms appear. This notion is clearly shown in several other autoimmune illnesses, which may represent the genetics of the host response and environmental factors. As a result, establishing a link between a viral infection and the development of an autoimmune illness may be difficult and obscure [84,86].

Infections are important environmental factors that affect the development of autoimmune diseases both positively and negatively. The underlying mechanisms are diverse and complex, and they will almost certainly differ among infections. It will be fascinating to determine if these processes and the infections can be related to polymorphisms in genes that predispose to or protect against the various autoimmune disorders. The recently discovered association between TLR2, TLR4, and TLR10 gene polymorphisms and asthma is worth noting here.

Data Availability

The data are kept with the main author. It was available upon request from the corresponding author.

Conflicts of Interest

Authors report no conflicts of interest related to this study.

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