Azhar Int J Pharm Med Sci 2025; Vol 5 (1):177-192.
Review Article

Open Access

Print ISSN: 2735-4598
Online ISSN: 2735-4601

Autoimmune Hepatitis: Insights into Classification, Pathogenesis, Diagnosis, and Therapeutic Strategies

Kawther Magdy Ibrahim[1] *, Hebatalla I. Ahmed[2], Laila Ramadan [1], Amany Balah [2]

[1] Department of Pharmacology & Toxicology, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt.
[2] Department of Pharmacology & Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.
***** Correspondence: e-mail: kawther-mohamed@eru.edu.eg

Article history: **Received** 12-02- 2024 **Revised** 08-05-2024 **Accepted** 11-06-2024

Abstract: Autoimmune hepatitis (AIH) is a multifaceted liver disorder characterized by immune-mediated inflammation, potentially leading to severe liver damage if left untreated. Despite an elusive etiology, it is believed to arise from a combination of genetic predisposition and environmental triggers, with a bimodal age distribution affecting individuals of all ages and genders. Classification efforts have delineated two main types based on autoantibody profiles, with genetic susceptibility in the human leukocyte antigen (HLA) region and environmental factors. AIH presents with a diverse clinical phenotype, ranging from asymptomatic cases to fulminant hepatitis leading to liver failure. Its manifestation can vary from acute to gradual or silent onset. Diagnosis relies on a combination of clinical, biochemical, serological, and histological criteria, with liver biopsy playing a pivotal role. Autoantibodies such as ANA and ASMA aid in diagnosis, while characteristic features such as interface hepatitis are discernible on liver histology. Animal models serve as indispensable tools in unraveling the pathogenic processes and immunology of AIH. Spontaneous and induced models provide valuable insights into T cell activation, hepatic damage, and the mechanisms underlying AIH. These models offer promising avenues for studying potential treatment targets and advancing therapeutic strategies for AIH. The management of AIH poses challenges due to the chronic nature of the disease and potential adverse effects of medications. Treatment strategies involve a balance between immunosuppression and minimizing drug-related complications. Liver transplantation may become necessary in a small percentage of cases, with regular monitoring playing a crucial role in evaluating treatment efficacy and adjusting therapy. This review provides a comprehensive examination of AIH, exploring its immunological mechanisms, clinical presentations, diagnostic criteria, animal modeling approaches, and recent therapeutic advancements.

Keywords: Autoimmune hepatitis; Pathogenesis; Diagnosis; Animal models of AIH; Management; De novo AIH.

1. INTRODUCTION

The most prevalent of the three disorders, autoimmune hepatitis, has been identified for more than 50 years and is curable when caught early. This illness can manifest as either chronic liver disease or acute hepatitis [1]. It is assumed that the illness originates from a lack of immunologic tolerance against hepatocytes in genetically susceptible individuals brought on by environmental stimuli, maybe through "molecular mimicry." [2]. The gradual deterioration of the liver parenchyma is a hallmark of the autoimmune liver disease known as autoimmune hepatitis, this inflammatory disease can result in severe liver necrosis and apoptosis, elevated serum transaminases, inflammatory cytokines, and failure if left untreated [3, 4].It is an immune-mediated hepatitis that Jan Waldenström first reported in 1950 [5]. T cells are the primary mediators of that [6]. It occurs when the body's immune system, which usually targets viruses, bacteria, and other pathogens, targets the liver [7]. While the precise etiology of AIH remains uncertain, it is thought to be a complex polygenic disorder resulting from a combination of genetic and environmental variables [4]. It can be identified in

Cite this article: Ibrahim, K, Ahmed, H., Ramadan, L., Balah, A., Autoimmune Hepatitis: Insights into Classification, Pathogenesis, Diagnosis, and Therapeutic Strategies. Azhar International Journal of Pharmaceutical and Medical Sciences, *2025; Vol 5 (1):177-192*. doi: 10.21608/aijpms.2024.380308

DOI : 10.21608/aijpms.2024.380308

individuals of any age and gender. Although women are primarily afflicted, men make up 25–30% of sufferers [8].

Autoimmune hepatitis may begin as an episode of acute hepatitis and in some cases progresses to cirrhosis, hepatocellular carcinoma, or death [8, 9], and in recent years, both its incidence and prevalence have increased [8]. Incidence rates for AIH vary from 0.7 to 2.0 per 100,000 people per year globally, while prevalence rates range from 4 to 25 per 100,000 people [10]. Many researches showed that autoimmune hepatitis exhibits a bimodal age distribution, with the first peak occurring between the ages of 10 and 30 years and the second peak occurring between the ages of 40 and 50 years [9]. Both the deterioration in hepatic tolerance and the autoimmune inflammation of the liver have unclear origins and mechanisms. Because of this, non-selective immunosuppression remains the cornerstone of treatment for AIH; there are presently no specialized or targeted medicines available [11].

2. CLASSIFICATION

There have been efforts to subclassify AIH based on the serologic autoantibody profile or genetic markers [12]. There are two types of AIH based on the expression of autoantibodies [13], and according to seropositivity: Type one AIH is distinguished by the presence of antinuclear antibodies (ANAs) and/or anti-smooth muscle antibodies (anti-SMA), it affects people of all ages, and the most prevalent type about 80% of all AIH cases [10, 14], whereas type two AIH (AIH-2) is distinguished by the presence of anti-liver-kidney microsomal antibody type one (anti-LKM1) or anti–liver cytosol type 1 antibodies (anti–LC) [9, 15]. The male-to-female ratio in AIH is between 1:4 and 1:6, which is similar to other autoimmune disorders where there is a noticeable prevalence of women [16].

3. PATHOGENESIS

In a genetically susceptible individual, autoimmune hepatitis is a complicated condition that is most likely caused by the combination of environmental factors and a trigger. This illness is complex and polygenic. Certain genetic polymorphisms or variations can increase or decrease an individual's chance of contracting an illness. Although the specific processes for the immunological tolerance to break down in autoimmune hepatitis are yet unknown [9]. As a result, breaking through self-tolerance in the liver can be more challenging than in other organs. A theoretical hypothesis explaining the pathophysiology of autoimmune hepatitis states that in a host that is genetically susceptible to the illness, an environmental stimulus triggers a cascade of T-cell-mediated responses [17], that result in an unregulated immunological attack against hepatocytes [13.] Furthermore, the most compelling example of such origins is the connection between AIH and a number of autoimmune disorders, such as systemic lupus erythematosus, autoimmune thyroiditis, colitis, and type 1 diabetes mellitus [10]. In conclusion it is believed that an imbalance in immune cell control, T-lymphocyte-mediated cell death, and an impaired immune response to foreign antigens brought on by a lack of tolerance to immunological stimulants form the pathophysiology of autoimmune liver disorders [8]. AIH can develop into a serious liver disease, and its causes are unclear and complicated. Consequently, it is critical to investigate the pathophysiology of AIH and look for viable and efficient therapy options [18].

3.1. Genetic susceptibility

Mendelian autosomal dominant, autosomal recessive, or sex-linked inheritance patterns are not observed in autoimmune hepatitis, which is categorized as a "complex trait." The inheritance process of a complex trait disease is unknown and involves one or more genes that interact with environmental factors to either increase or decrease the trait's risk [19]. Autoimmune hepatitis has been strongly associated with genes from the human leucocyte antigen (HLA) [8]. Region on the short arm of chromosome 6 [20]. Nevertheless, because up to 30% of healthy Caucasian individuals have HLA predisposing to AIH, this is insufficient to initiate the illness [21]. Different HLA-subtypes contribute different relative risks in different ethnic groups. More than half of the patients in the Caucasian population have the extended HLA haplotypes DRB1*0301 and DRB1*0401, which are closely linked to the disease, although the haplotype DRB1⁄1501 seems to be protective [22].

3.2. Environmental Factors

The liver is constantly exposed to harmful antigens, poisons, cancerous cells, and food antigens because of its location and function, and the hepatic immune system needs to be tolerant of these things or able to react to them [8]. The main pathogenic mechanism is thought to be a lack of tolerance to the patient's own liver antigens [23]. Environmental exposures play greater roles than genetics in shaping the immune repertoire [24], and specific environmental factors in vulnerable people including viral infections [13, 21], alcohol, and changes in the composition of the intestinal microbiota. Importantly, in addition to the Hepatitis A vaccine and medications such as infliximab, minocycline, atorvastatin, diclofenac, isoniazid, αmethyldopa, nitrofurantoin, and propylthiouracil, herbal remedies like black cohosh

can cause autoimmune liver disease or classical autoimmune hepatitis [8, 25]. Identifying an infectious agent may be hard because the trigger or triggers of autoimmune hepatitis may be part of a phenomena known as the "hit-and-run phenomenon," in which induction occurs several years before overt autoimmune illness [17]. Additionally, the requirement for recurrent exposure to the same or similar antigens prior to the onset of autoimmune hepatitis may obstruct the identification of a causal event [15].

Although the precise cause of drug-induced AIH is unknown, a number of pathways may be involved. The hepatotoxic action of these compounds is one potential reason. Moreover, medications may cause AIH by upregulating the expression of immunoregulatory and P450 proteins, among other proteins. Drugs that function as hapten and alter liver proteins to make them immunogenic constitute another pathway. Moreover, the production of medication metabolites that attach to proteins and create antigenic complexes may facilitate the production of autoantibodies. More specifically, CYP1A2 and CYP2A6 may be involved. Another method that medicines might cause AIH is via sensitization of lymphocytes. Crucially, stopping the offending substance may cause drug-induced AIH to improve, highlighting the need of early detection [15, 25].

4. CLINICAL PRESENTATION

In both adult and pediatric contexts, the disease's clinical phenotype can be wildly varied, ranging from asymptomatic cases, which are typically seen in individuals with coexisting autoimmune diseases to fulminant hepatitis leading to liver failure. Patients who do not exhibit symptoms share a similar liver histology as those who do, and treatment is necessary to prevent the illness from getting worse [21]. Three fourth of the patients are female, and the majority are in their second, fifth, or sixth decade. There are three main ways in which autoimmune hepatitis manifests clinically: acute onset, gradual onset, and silent onset. Here is a summary of these patterns: [2].

In adults as well as in children and adolescents, the most common pattern of autoimmune hepatitis globally now appears to be acute onset [26]. It commonly manifests as jaundice, occasionally with a prolonged international normalized ratio, and transaminase values that are five to ten times higher than the upper limit of normal. The diagnosis is confirmed by the presence of elevated IgG concentrations, common autoantibodies such as SMA, anti-LKM1, anti-LC1, and anti-SLA/LP, and liver histology with characteristics of interface hepatitis, once all other potential causes of liver damage have been ruled out. abrupt severe or subfulminant hepatitis is a rare presentation for patients, and it can occasionally lead to abrupt liver failure [27]. It is best to promptly refer this unusual kind of patient to a liver transplant facility. The non-specific symptoms of gradual onset include tiredness, arthralgia, malaise, amenorrhea, and in a small number of instances, the signs and symptoms of hepatic cirrhosis [17].

When a patient has asymptomatic onset, they do not exhibit liver-related signs or symptoms. Instead, they are evaluated when unintentionally altered liver function tests occur or when other medical conditions—particularly extra-hepatic autoimmune disorders—such as thyroid disease, celiac disease, and rheumatologic conditions [28].

5. DIAGNOSIS

The presence of specific clinical signs and the rule out of other chronic liver diseases, such as hemochromatosis, alpha 1 antitrypsin deficiency, fatty liver disease, alcohol-linked liver disease, viral hepatitis, or drug-induced hepatitis, are necessary for the diagnosis of AIH [25]. There are no distinctive diagnostic characteristics for AIH [29], the absence of serum autoantibodies makes diagnosis highly challenging [16], and no single disease-specific test exists [11], but histopathological assessment of liver tissue is crucial for staging and grading in addition to treatment tracking [12]. The inability to detect at an early stage causes therapy to be delayed. As a result, more research has looked into AIH biomarkers that may be used to get a diagnosis early [30]. The diagnosis of AIH is depend on combination of clinical, biochemical, serological and histological characteristics, each of which can be seen separately or together in different liver disorders [13]. Furthermore, it is important to carefully consider both personal and family history because autoimmune hepatitis has a hereditary propensity and, like other autoimmune illnesses, is linked to a number of autoimmune problems [22].

5.1. Laboratory abnormalities

Autoimmune hepatitis is suggested by a patient with elevated level of alanine aminotransferase (ALT) and aspartate aminotransaminase (AST), positive autoantibodies in the blood (IgG level) with normal levels of (IgA) and (IgM) [22]. But not every one of these lab results has to apply to a particular individual [31]. It's important to screen out other liver disorders such viral hepatitis, genetic, metabolic, and cholestatic liver diseases that might mimic AIH [32]. Hypergammaglobulinemia is the cheapest of these screening tests [22]. The differential diagnosis must

also take drug-induced liver injury (DILI) into account. The distinction between DILI with characteristics of AIH and actual AIH [13]. Takes into account the patient's medical history and the results of any necessary laboratory tests, such as the polymerase chain reaction for the hepatitis B, C, and E viruses, because DILI can resemble, cause, or disclose AIH [21, 33]. Occasionally, patients may receive a diagnosis following the unintentional finding of an abnormal liver function test [34].

5.2. Autoantibodies

AIH is characterized by the presence of circulating autoantibodies such as LKM-1, ASMA, and ANA. They aid in the diagnosis and categorization of AIH into types 1 and 2 [20, 35]. The most prevalent autoantibodies in AIH are ANA, which are fairly nonspecific since they may be seen in both healthy persons and a wide range of disorders. The second main class of antibodies that has shown promise in the diagnosis of AIH is ASMA. They are more specific than ANA, although being less common [31]. It is advised to retests for antibodies because they may not appear during acute AIH and may only manifest later in the illness. However, in cases of acute severe hepatitis of any sort, including DILI, autoantibodies (ANA and SMA) are often seen [11]. Anti-LKM1 are frequently found when ANA and SMA are not present, and this finding has supported their evaluation after ANA and SMA testing. Additionally, among adults in North America, anti-LKM1 has a poor sensitivity for AIH (1%), therefore it is recommended to test these individuals only after it has been established that they do not have ANA or SMA. In 7%–22% of individuals with type 1 AIH, soluble liver antigen (anti-SLA) antibodies are found, and these antibodies have a high specificity (99%) for the diagnosis. In 14%–20% of patients, anti-SLA has been the only indicator of AIH; it has been linked to severe illness and recurrence upon medication cessation. Antibodies against liver cytosol type 1 (anti-LC1) are mostly seen in children with severe liver illness and are seen in 32% of individuals with anti-LKM1 [24].

5.3. Liver Biopsy

At the moment, a liver biopsy is required to diagnose AIH [13]. A liver biopsy is not only necessary to confirm the diagnosis of AIH, but it also aids in determining the severity of the illness, helps determine the dosage of immunosuppressive medication, and helps determine when the patient should have a liver transplant. A liver biopsy may be used independently to differentiate AIH from other liver disorders and is generally regarded as a crucial component in the differential diagnosis of liver disease. Moreover, liver histology is essential for both early diagnosis and long-term follow-up because it permits disease staging, therapeutic monitoring, and evaluation for inflammation and fibrosis. It is also a requirement for using the streamlined AIH score [34]. Individual histological criteria are not available to support the diagnosis of AIH. The histopathological characteristic of AIH is interface hepatitis, also known as piecemeal necrose, which is caused by inflammatory infiltration and erosion of the hepatic parenchyma at the portal tract junction. The hepatic mesenchymal cells that make up the infiltrates are accompanied by lymphocytes, plasma cells, and histiocytes [31].

According to current guidelines, liver biopsy should be done as soon as a patient first presents; nevertheless, bleeding risk may be higher in individuals who have acute liver failure and weakened coagulation. In this case, plugged or transjugular biopsies might be a good substitute method for obtaining a liver material for histologic analysis. Exploratory laparoscopy liver biopsy surgery can be a rather invasive procedure that calls for general anesthesia [34].

6. ANIMAL MODELS OF AIH

Several animal models are created to provide further insight into the pathogenic processes and hepatic immunology of AIH. Finding new treatment targets for AIH will be made easier with the knowledge these models provide [36].

6.2. Spontaneous Models

The first mouse model of spontaneous lethal AIH is said to be NTxPD-1−/− mice, which resemble acute-onset AIH that manifests as fulminant hepatic failure in people. PD-1-mediated signaling and naturally occurring regulatory T (Treg) cell loss occur simultaneously in NTxPD-1−/− mice, resulting in widespread lobular necrosis, ANA generation, and T cell activation and infiltration into the liver parenchyma. Similar to AIH in humans, dexamethasone treatment prevents the illness from progressing, but stopping the drug causes AIH to recur [37]. According to this paradigm, inflammatory cytokines like TNF-α and INF-γ produced by CD8+ T lymphocytes entering the liver contribute to liver damage and are essential for the development of illness [38]. Nevertheless, these mice begin to die at the age of just two weeks of age, with the majority passing away by 4 weeks, as a result of the extensive damage of the liver parenchyma. In conclusion, The NTxPD-1−/− mice provide the initial rodent model for spontaneous serious AIH; however, due to their short lifespan, they cannot be used in deeper mechanistic research [37].

6.2. Models Developed by Replicate Antigens

6.2.1. Concanavalin A–Induced Hepatitis

Concanavalin A (Con A) activates antigen-nonspecific T lymphocytes and macrophages in a dose-dependent manner, causing acute immune-mediated hepatic damage. Con A mostly accumulates on Kupffer cells and liver sinusoidal endothelial cells (LSECs) where it binds to mannose-rich glycoproteins, which can further cause T cells to undergo solid cellular arrest [37]. According to recent research, Con A can activate natural killer T (NKT), CD4+ T cells, macrophages, and APCs.

It can also promote the release of proinflammatory cytokines in mice, such as various chemokines, interleukins (IL-6, IL-12, and IL-18), and tumor necrosis factor-α (TNF-α) [39]. T cells, particularly NKT cells, release pro-inflammatory cytokines like IFN-γ and TNF-α, which then attract and activate other cells and cause LSECs and hepatocytes to undergo apoptosis. IFN-γ has the potential to enhance TNF-induced DNA fragmentation and hepatotoxicity via activating TNF receptors on hepatocytes [40, 41]. In conclusion, Con A-induced hepatitis is a useful model for the highly selective activation of T cells and has a wide range of applications in the study of T cell function processes in AIH. It is an acute, as opposed to a chronic, model of liver damage, and it is cytokine-dependent and antigen-independent [37].

6.2.2. CCl_4-induced liver injury models

Furthermore, substances like CCl4 are more likely to cause a non-specific immune response even though they might cause liver inflammation and impair immunological tolerance [39]. It has ability to cause acute or chronic hepatitis. Because oral CCl4 treatment activates leukocytes and immune-mediated liver injury, it is considered an experimental model of autoimmune hepatitis. Oral administration of CCl4 results in the activation of leukocyte and immune-mediated liver damage, and is thus regarded as an experimental model of AIH.

Although CCl4 efficiently stimulates the production of pro-inflammatory cytokines, disrupts liver tolerance and even triggers autoimmune responses in livers, a few studies have pointed out that CCl4 may induce a non-specific liver inflammation rather than a typical AIH [39]. Although CCl4 does not directly cause hepatotoxicity, its metabolites CCl3 and OOCCl3, which are produced by cytochrome P450-dependent monooxygenases in hepatic parenchyma cells, do [42]. which causes oxidative stress and membrane damage [43].

6.2.3. α-Galactosylceramide–Induced Hepatitis

α-Galactosylceramide (α-GalCer), is a synthetic glycolipid that invariant NKT cells may identify via CD1d. α-GalCer has the ability to cause hepatic damage that is similar to acute AIH in humans [44]. Furthermore, pretreatment with α-GalCer aggravated D-GalN-mediated AIH in mice [39]. α-GalCer-injected mice exhibit elevated blood levels of ALT, AST, and ANA along with necrosis of hepatocytes and lymphocytic infiltration. It induced liver damage is mediated by TNF-α but not by Kupffer cells [37]. TNF-α has a key role as a mediator in α-GalCer-induced hepatic damage, and it also contributes to the upregulation of Fas ligand (FasL) on NKT cells caused by α-GalCer [45].

6.3. Models Triggered by Liver Autoantigens

6.3.1. Hepatitis Induced by Liver Homogenate

Extracts from liver have the ability to effectively break down liver tolerance and cause the clinical manifestations of AIH, also known as experimental autoimmune hepatitis. Mice with piecemeal necrosis and the infiltration of mononuclear cells, primarily lymphocytes, in portal regions are given a monthly injection of syngeneic liver homogenate and an adjuvant polysaccharide of Klebsiella pneumoniae 03:K1 [46]. A different model is developed by injecting 100,000×g of syngeneic liver homogenate (S-100) emulsified in Freund's adjuvant intraperitoneally into male C57BL/6 mice. Inflammatory infiltrates, hepatocyte necrosis, and the production of T lymphocytes specific to the S-100 protein are the outcomes of this [37]. This simple technique has been extensively employed in the investigation for the processes behind AIH, such as the critical function of mitogen-activated protein kinase p38 [47].

7. DRUG- INDUCED AIH LIKE INJURY

Drug-induced liver injury can mimic AIH, Although uncommon, linked to over a thousand medications or dietary/herbal supplements [48]. 2%–17% of individuals with typical AIH symptoms have been linked to an erratic idiosyncratic or hypersensitive medication response [24]. The usual scenario is a latency period following first drug exposure, during which time autoimmune symptoms, including hepatitis, may not manifest for more than three months, or in rare circumstances, for many years. Patients may exhibit symptoms such as decreased appetite, jaundice, nausea, and abdominal pain, particularly in the right upper quadrant. Laboratory results that indicate autoimmunity include high levels of immunoglobulin, antinuclear antibodies, antismooth muscle antibodies, anti-LKM antibodies,

and infrequently antimitochondrial antibodies. Evidence of damage to other organs, including as the kidneys, lungs, GI tract, and joints, may also be seen in addition to the liver. While there is a chance for an acute presentation that results in liver failure, the majority of the time the disease is extended and results in a chronic autoimmune hepatitis-like syndrome [49]. While most cases of DILI resolve on their own when the offending medicine is stopped, it can also manifest with any phenotype of acute or chronic liver disease and have serious repercussions, such as chronic liver damage, liver transplantation, or even death [48].

7.1. Alpha-methyldopa

Alpha-methyldopa is used to treat both essential and gestational hypertension by centrally reducing sympathetic tone. It is common for DIAIH to be associated with liver damage, increases in IgG and autoantibodies ANA and anti-smooth muscle, and it can take up to 24 months for full recovery [48]. With enhanced rich plasma cell staining and interface hepatitis, the histology may resemble that of AIH. Although fibrosis can differ and be associated with mild to severe steatosis, at least two instances have reported cirrhosis when alpha-methyldopa was not quickly stopped [50]. Nevertheless, methyldopa may induce hepatic necrosis through an immunological reaction, and there is evidence to support this theory, including the lack of a dose relationship and animal toxicity. Additionally, a clinical study revealed that some patients who received methyldopa also experienced fever or rash in addition to hepatitis, further pointing to a hypersensitivity reaction [51].

7.2. Fibrates

A family of drugs known as fibrates is used to treat hypertriglyceridemia and dyslipidemia. Although fenofibrate has seldom been linked to acute liver injury, chronic liver injury is far more prevalent and frequently manifests as DI-AIH. Fibrate-associated DI-AIH is usually diagnosed in the context of elevated blood immunoglobulins and high-titers of ANA [48]. Results vary since cases of cirrhosis confirmed by biopsy have been reported [52].

7.3. Statins are HMG-CoA reductase inhibitors.

There is ongoing controversy over the hepatotoxic potential of statins, which are inhibitors of the enzyme Hydroxymethylglutaryl-coenzyme A (HMG-CoA). Recent modifications to regular liver related enzyme monitoring as a screening method for IDILI detection reflect this [53]. Statins cause hepatotoxicity; however the precise mechanism is unclear. Because they disrupt the mitochondria, statin therapy can lead to a significant rise in mitochondrial superoxide production and subsequent damage of the mitochondria. This can be hepatotoxic [51].

7.4. Hydralazine

The antihypertensive medication hydralazine has been associated with two forms of liver injury: acute and chronic. The acute form of liver injury often coexists with a lupus-like disease characterized by positive ANA and autoimmune characteristics. This syndrome can appear anywhere from five to twenty-six months into treatment [48]. According to theory, the mechanism behind liver damage is due to its metabolism into an immunologic adduct, which might induce immunoallergic hepatitis, delayed lupus-like disease, or autoimmune hepatitis-like syndrome. When using hydralazine, liver damage can result in a variety of reactions ranging from a moderate immunologic reaction that goes away on its own to liver failure necessitating liver transplantation [54].

7.5. Nitrofurantoin

In the 1950s, the antibiotic nitrofurantoin was developed to treat both acute and persistent lower urinary tract infections. As early as the 1960s, case reports detailed nitrofurantoin-induced acute hepatitis. It is among the more often prescribed drugs for DIAILD. A 2008 DILIN research looked at 300 individuals who had unique DILI. Amoxicillin/clavulanate was the most often implicated medicine (n = 23), followed by trimethoprim-sulfamethoxazole (n = 13), isoniazid (n = 13), and nitrofurantoin (n = 13) [55].

7.6. Minocycline

Since 1972, minocycline, a tetracycline derivative, has been used to treat a range of illnesses. Acne vulgaris is one of the primary indications for therapy and may need long-term usage. There have been several reported minocycline-induced disorders, such as autoimmune hepatitis, drug-induced lupus, serum sickness, and vasculitis [56]. Minocycline-induced hepatotoxicity has been reported in three different patterns. The first is hepatic steatosis, which develops after intravenous administration of a large dosage. This is believed to be a direct hepatotoxic effect that is dose-related and has also been seen with tetracycline. Within 35 days of commencing minocycline, immunoallergic symptoms (rash, eosinophilia) characterize a second response. The third presentation happens later (on average, a year later), mimicking AIH [57].

7.8. Tumor necrosis factor-alpha (TNF-α) antagonists

Biologically active monoclonal antibodies against TNF-α, such as adalimumab and infliximab, are given to treat inflammatory disorders mediated by the immune system, such as rheumatoid arthritis and inflammatory bowel disease [48]. Although hepatitis B reactivation or iDILI have been more strongly associated with biologically active monoclonal antibodies to TNF-α, there is mounting evidence that suggests a connection with DI-AIH. Greater hepatocellular damage and a longer latency time were features of the autoimmune phenotype. Corticosteroid treatment was given to twelve patients. After DILI resolution, treatment with an alternate TNF-α antagonist appears to be well tolerated [58].

8. MANAGEMENT

Treatment Goals

The ultimate goal of AIH treatment is managing hepatic inflammation towards histological clearing, promoting the regression of fibrosis, preventing disease progression, and initial symptom relief [32]. Given the lifetime medication and possible adverse effects, clinical care of AIH can also be a difficult process [59]. Usually, immunosuppressive medications and lifestyle changes to promote liver health are used in the therapy of AIH [32], thereafter long-term remission state maintenance. The ideal way to do this would be to minimize the corticosteroid dosage, with the ultimate objective being complete withdrawal [60]. Here are some key aspects of AIH management:

8.1. Medications:

8.1.1. Standard Frontline Treatment with Corticosteroids and Azathioprine

Unfortunately, there are presently few and non-specific treatment choices for this kind of hepatitis, which remains a significant clinical problem [6]. Because the mechanisms of AIH are not fully understood [61], there are no more effective drug choices available than glucocorticoid and immunosuppressive combination therapy (corticosteroids, azathioprine, etc.) [62]. As soon as the disease was identified as an autoimmune ailment, early observations showed that patients had a favorable reaction to steroids, which ultimately saved their lives [22]. The first medication of choice for AIH maintenance treatment is azathioprine [59], which achieves remission in 80% of cases [5]. Azathioprine is converted into 6-mercaptopurine subsequently blocking purine metabolism and DNA synthesis [63]. The American Association for the Study of Liver Diseases 2019 (AASLD) practice guidelines and guidelines updated the first-line treatment recommendations, suggesting either prednisone monotherapy (40–60 mg/day) or a combination of prednisone (20–40 mg/day) or budesonide (9 mg/day) and AZA (50–100 mg/day). According to the 2015 European Association for the Study of the Liver (EASL) guidelines, the first course of therapy should consist of 0.5–1 mg/kg/day predniso(lo)ne, and an additional 50 mg/day of AZA. In the same way, the AASLD recommends that the patient be observed for two weeks prior to starting AZA in order to assess thiopurine-S methyl transferase (TPMT) levels and confirm the patient's steroid response. This will help prevent AZA-induced hepatitis. Single nucleotide polymorphisms in TPMT genes that result in loss of enzymatic activity expose patients, especially those descended from Europeans and Africans, to thiopurine-related toxicity. TPMT is an enzyme that anabolizes thiopurines, including AZA [29]. Pregnancy is safe when using azathioprine. According to a recent large retrospective French study, exposure to azathioprine during the first trimester is not associated with an increased risk of birth abnormalities, and exposure during the third trimester does not raise the chance of pre-term delivery, which is most likely caused by the mother's sickness [21], but most often causes serious adverse effects, such as leukopenia and gastrointestinal problems [34], increase the risk of developing infections such as tuberculosis, and bone marrow suppression, the primary cause of drug withdrawal [29], and it should not be started in patients with cholestasis or elevated bilirubin until the bilirubin falls below 6 mg/dl [29]. Up to 40% of patients may relapse as a result of poor compliance or after trying to stop therapy [29]. Thus, ongoing maintenance treatment may be required forever [16].

Within the first year of treatment, every AIH patient should aim for steroid-free therapy as a means of preventing problems connected to steroid use. Several steroid side effects, including striae, acne, and moon-shaped faces [31]. Drug withdrawal or dose reduction are necessary in cases of weight gain, diabetes mellitus, hypertension, emotional instability, and even psychosis. Eighty percent of patients have side effects due to steroids after two years of medication [63]. However, when azathioprine is given in combination therapy, this occurs less commonly. Prior to starting steroid treatment, it is recommended to test bone density in order to prevent the onset of osteoporosis. Additionally, patients should take vitamin D pills and consume adequate calcium-rich foods [59]. The main adverse effects of azathioprine include abnormal liver tests and

cytopenia, which might be hard to differentiate from the underlying disease activity of AIH [31].

8.1.2. Secondary and Alternative Therapies

The goal of second-line therapy for AIH is to use prednisone (lo)ne/azathioprine to manage drug intolerance, refractoriness, and insufficient biochemical response [32]. For patients with AIH, the AASLD suggests a trial of mycophenolate mofetil (MMF) over tacrolimus as the first second-line medication because of its better ease of administration and side-effect profile [20].

8.1.2.1. Mycofenolate Mofetil (MMF).

Inosine monophosphate dehydrogenase is the enzyme that limits the rate of purine synthesis. The next-generation noncompetitive inhibitor of this enzyme is Mycofenolate mofetil. Because purine synthesis is the primary means of supporting T and B cell proliferation, as opposed to other cell types, MMF functions as an efficient antiproliferative immunosuppressant medication. MMF has become the primary antirejection medication in solid organ transplantation, surpassing azathioprine. Additionally, MMF has proven to be an effective second-line or salvage treatment in individuals with azathioprine intolerance or corticosteroid resistant illness [11, 34, 59]. A meta-analysis revealed that the most commonly given second-line therapy was MMF with prednisone, which resulted in histological remission in 89% of the patients [29]. Furthermore, according to reports, MMF helped patients achieve histological remission, steroid sparing, and transaminase normalization [64]. Adults typically begin taking it at 500 mg twice day and escalate to 1000 mg twice daily if tolerated; children start taking it at 5 mg/kg twice daily and can take up to 20 mg/kg twice day [21]. Conversely, MMF can cause gastrointestinal distress and should not be administered to a pregnant woman because of its teratogenicity. This is significant because AIH primarily affects younger women [59]. From an economic perspective, MMF appears to be six to seven times more cost than azathioprine, leading to significant treatment expenditures for individuals whose course of therapy is not determined [34].

8.1.3. Third-line therapy

Referral centers should handle the 10-15% of AIH patients who are not easily threatened [21].

8.1.3.1. Calcineurin Inhibitors:

Among the class of calcineurin inhibitors (CNI) utilised as a rescue medication for adult patients with AIH are cyclosporine A and tacrolimus [21], Since the 1990s several case reports and case series have been published regarding treatment of AIH with cyclosporine, at 2-5 mg/kg [65]. Act by preventing the nuclear production of proinflammatory cytokines like interleukin-2 and suppressing activated T cells by inhibiting the intracytoplasmic enzyme calcineurin [66], and are widely used as immunosuppressive medications for patients of solid organ transplants. Additionally, they have proven to be an effective alternative treatment for AIH patients who do not react to steroids and azathioprine. Cyclosporine A has been associated with serious side effects, including nephrotoxicity, neurotoxicity, infection, and an elevated risk of cancer. with prolonged usage. Additionally, evidence from animals suggests that Cyclosporine A may not be the best drug to treat AIH since it may potentially worsen immunosuppression and encourage autoimmune [34]. Therefore, prescriptions should only be written by medical professionals who have extensive expertise with these medications [59].

8.1.3.2. Tacrolimus

Similar to cyclosporine, TAC also prevents T-cell activation by blocking intracellular calcineurin activity [65]. Tacrolimus has been used as a first-line and rescue therapy for adults and children with AIH. The evidence that is now accessible is of poor quality. In patients who are intolerant to traditional first-line therapy or do not respond well to it, tacrolimus was shown to be as effective as MMF as a second-line treatment, according to a recent retrospective multicenter research. However, tacrolimus should only be used as a third-line therapy due to its toxicity. Some side effects include dermatitis, thrombocytopenia, mouth or leg ulcers, proteinuria, hyperlipidemia, and decreased immunity to infection [21]. The therapeutic range and dosage were different among the aforementioned investigations, with target blood levels generally residing around 6 ng/ml and dosages typically ranging from 2 to 6 mg/day [65].

8.1.4. Biologicals

8.1.4.1. Rituximab

Though AIH may be considered a T cell-mediated autoimmune disease, monoclonal B cell depleting antibody rituximab has shown promising treatment outcomes in refractory cases of the condition [67]. Rituximab interacts to the cell-surface antigen CD20, which is produced by B lymphocytes. These cells experience cytotoxicity from CD20 upon binding, but the exact mechanism is still unknown. It probably involves a variety of methods, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis

induction. Consequently, CD20 therapy results in B-cell depletion and immune response impairment, making it a viable medication option for the management of several autoimmune disorders [68].

8.1.4.2. Infliximab

One type of chimeric monoclonal antibody that targets TNF-α is infliximab. The antibody can block the biological activity and signals of TNF-α by forming stable complexes with both soluble and membrane-bound TNF. TNF- α is a critical regulator in immune cell activation and migration through gene expression of chemokines, cytokines, and toxic molecules, including reactive oxygen species. The antibody was created for rheumatoid arthritis and Crohn's disease, but it has also demonstrated efficacy and encouraging clinical outcomes in a variety of autoimmune conditions, including psoriasis, sarcoidosis, graft versus host disease, and many more [65]. Infliximab can cause a number of additional immune-mediated illnesses as well as signs of hepatotoxicity that mimic AIH. Because of this, it should only be used sparingly in specialized facilities with extensive training in AIH monitoring and treatment [34, 69].

8.1.5. Novel therapeutic target

8.1.5.1. Toll-like receptor 4 antagonist.

The family of cell surface receptors known as pattern recognition receptors includes toll-like receptor 4. It raises the levels of proinflammatory cytokines IL-1β, IL-6, and TNF-α when it binds to ligands and initiates intracellular signaling through NF-kB and MAPK.

Following the demonstration of anti-inflammatory and hepatoprotective characteristics in animal models of AIH, the TLR4 antagonist JKB-122 has entered a phase II clinical study (NCT02556372), the results of which have not yet been made public [21]. According to recent reports, pre-treating LD NX before administering Con A greatly reduced all hepatic damage indicators and enhanced liver function via altering the TLR4/NF-κB and Nrf2/HO-1 pathways [70].

Thus, blocking TLR4 expression and inhibiting the NF-κB pathway's activation might potentially be therapeutic targets for hepatitis caused by T cells [71].

8.1.5.2. DURATION OF TREATMENT

While the ideal duration of care is uncertain, it is advised to get therapy continuously for at least three years. Treatment should only be stopped if a subsequent liver biopsy sample demonstrates that the inflammatory abnormalities have resolved. As their fluctuations correspond with disease activity, measuring autoantibody titers and IgG levels is a valuable technique for tracking response to therapy. When other tests are normal after a protracted (≥2 years) period of stability, patients with cirrhosis who have a persistent rise of their blood IgG level are not banned from stopping their therapy [24]. For AIH patients who react well to immunosuppressive therapy, the long-term prognosis is favorable; most of these people may lead normal lives while taking low-dose medications [73].

8.1.5.2. Liver transplantation (LT)

Liver transplantation (LT) is indicated in 3%–5% of cases in the US due to autoimmune liver disorders (ALDs), which include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC) [74]. Due to abrupt onset autoimmune hepatitis that quickly progresses to severe liver failure or end-stage liver disease and accompanying consequences, such as hepatocellular cancer, liver transplantation may be necessary [2]. Needing for LT cannot be determined by a single factor; however, patients who exhibit necrosis on histology, a higher Model of End-Stage Liver

troughs have not been examined Disease (MELD) score upon administration, and no improvement in bilirubin and International Normalized Ratio (INR) levels during the first few days of steroid treatment are more likely to require an urgent transplant [34]. Liver transplantation is eventually required for 10%–20% of people with AIH [75]. For patients who arrive with acute liver failure, liver transplantation is a potentially life-saving surgery.33, despite the fact that LT represents a life-saving option [13], for patients presenting with acute fulminant liver failure which is unresponsive to steroid treatment and patients with end stage chronic autoimmune liver disease with a MELD Score > 15 or higher [9, 34, 76], such cirrhosis or hepatocellular carcinoma (HCC) [13], and in case of non-responsiveness to drug treatments [7].

Five years following liver transplantation, 36%–68% of patients had a recurrence of AIH [76]. Moreover, shortage of liver donors, immunological suppression [72], high costs, long waiting period for LT, the high risk of infection following surgery [61], such highly deadly fungal infections that cause graft loss and death [3].

Table 1. Overview of current status of various treatments for autoimmune hepatitis, dosing, Major/characteristic side effects, and Indication.

Drug	Dosing	Major/characteristic side effects	Indication	References
Prednisolone	40–60 mg/day	Striae, acne, moon-shaped faces, weight gain, diabetes mellitus, hypertension, emotional instability, and even psychosis	first-line therapy mono or combination	29, 65
Azathioprine	start 50mg/day, max. 1-2 mg/kg/day	Leukopenia, gastrointestinal problems, increased risk of infections (e.g., tuberculosis), and bone marrow suppression	first-line therapy (combination)	34, 65, 72
Mycofenolate Mofetil	1,5-2g/day	Gastrointestinal distress. - Contraindicated in pregnancy due to teratogenicity. - Higher cost compared to azathioprine.	second-line therapy in case of azathioprine intolerance or first line alternative to azathioprine	59, 65
Cyclosporine	2-5 mg/kg/day	Infection, nephrotoxicity, neurotoxicity, and increased cancer risk with prolonged use.	alternative to tacrolimus in specialist center	34, 66
Tacrolimus	2-6 mg/kg/day (target blood level around 6 ng/ml)	Hyperlipidemia, mouth or leg ulcers, thrombocytopenia, proteinuria, dermatitis, and lowered immunity to infection	second-line therapy in case of azathioprine treatment failure	21, 65
Rituximab	1000mg i.v. qw2	Infusion related reactions, cardiotoxicity, dermatitis,	third-line therapy in specialist center	65
Infliximab	5mg/kg i.v. at day 0, week 2, week 6, then every 4-8 weeks	Induce immune-mediated illnesses and hepatotoxicity.	third-line therapy in specialist center	34, 65, 69

Compared to other liver illnesses, autoimmune hepatitis is associated with a higher incidence of acute and chronic rejection following liver transplantation [24], and other stubborn postoperative problems restrict its use [61]. After liver transplantation, the choice of immunosuppressive and immunomodulating drugs will probably have an influence on how frequently AIH recurs.
For instance, it has been observed that low-dose steroid therapy can stop AIH from recurring in the liver graft.

Additionally, the transplant experience can be used to draw conclusions about the effectiveness of second- or third-line therapy choices for AIH [11]. As a result, studies in AIH pathophysiology and the exploration of alternative candidate medications with potential activity and minimal toxicity is necessary.

9.TREATMENT STRATEGIES FOR RECURRENT DISEASE

According to the most recent AASLD guidelines, the optimal course of treatment for recurrent AIH is to continue a CI while adding AZA or MMF and reintroducing steroids. The target CI troughs have not been examined, but if possible, it could make sense to raise the trough goal. Consider switching CIs, substituting MMF for AZA, or vice versa, or replacing CIs with sirolimus if serum transaminases do not normalize [74]. The hazards of steroids exceed any possible advantages, which is why the AASLD recommendations conditionally recommended considering a progressive withdrawal of steroids following transplant. Although budesonide has not been examined in the posttransplant population, it has been utilised as a first-line therapy for mild-to-moderate AIH in conjunction with AZA. Although they have been effectively utilised in recurrent AIH post-LT, rituximab and plasmapheresis are not now considered standard of therapy [24, 77].

9.1. De Novo AIH

De novo AIH denotes the development of AIH in a patient transplanted for a disease other than AIH [24]. Theoretically, among those who are genetically prone to autoimmune illnesses, de novo AIH represents an unusual type of rejection [78]. After LT, this syndrome was first reported in children, mostly in individuals who had biliary atresia. De

novo AIH has now been identified in individuals receiving transplants for different aetiologies, and one series found that patients with primary biliary cholangitis (PBC) had a greater frequency of the condition [79]. Children are more likely than adults to have it (5%–10% vs. 1%–3%).The clinical manifestations of both autoimmune and recurrent hepatitis are comparable in de novo hepatitis. Elevated levels of IgG, alanine aminotransferase, and aspartate aminotransferase are seen in serum. The discovery of recently generated autoantibodies is one of the most notable characteristics of de novo autoimmune hepatitis. Anti-NKM-1, anti-LC, antibodies to gastric parietal cells, ANA, anti-mitochondrial, anti-SMA, and atypical anti-liver/kidney cytosolic antibodies targeting the antigen glutathione-S-transferase T1 (GSTT1) may be positive in patients with de novo autoimmune hepatitis [76]. The liver produces the enzyme GSTT1, or glutathione S-transferase theta 1, which is involved in the metabolism of xenobiotics and De novo AIH may arise if the donor and recipient have different GSTT1s [80].

Moreover, interface hepatitis involving lymphocytes and plasma cells is the primary histological characteristic of de novo autoimmune hepatitis. Spotty necrosis, portal fibrosis, and bile duct damage are further histological characteristics [76]. Although the outcomes of treating de novo autoimmune hepatitis are encouraging, improper management of these individuals can lead to poor outcomes including cirrhosis and graft loss. Early detection and treatment of this illness are therefore crucial. The cornerstone of therapy for de novo autoimmune hepatitis remains prednisone (lo)ne, with or without AZA. If these drugs elicit no response, MMF may be used in lieu of AZA [79].

9.2. RISK FACTORS FOR DE NOVO AUTOIMMUNE HEPATITIS

De novo AIH is more common in recipients of female grafts or older donors, indicating that the allograft may carry a risk for de novo illness. Atypical serum autoantibodies, most of which are antibodies against glutathione-S-transferase T1 (anti-GSTT1), have also been linked to de novo AIH. Indeed, the mismatching of donor and recipient for the GSTT1 genotype has been proposed as essential for the appearance of anti-GSTT1 and the development of de novo AIH [79]. Acute rejection episodes and antiviral medication for hepatitis C infection after liver transplantation are two further possible risk factors [81].

10. MONITORING AND REGULAR CHECK -UP

Liver function monitoring on a regular basis is essential for managing AIH. Usually done every few months at first, and then less frequently as the condition stabilizes, blood tests are used to evaluate liver enzymes, liver function, and immunological indicators such immunoglobulin levels. Monitoring assists in assessing symptoms, determining the efficacy of the drugs, identifying any possible adverse effects or illness flare-up, and customizing therapy [59]. Promising pharmacologic therapies have been emerged to achieve optimal management of AIH. These days, a renewed focus on complementary and alternative medicine has sparked a fresh wave of research to find more effective drugs with fewer adverse effects.

11. CONCLUSION AND FUTURE ASPECTS

In conclusion, Autoimmune hepatitis is a liver condition known for its highly favorable response to treatment, but it still poses numerous unresolved questions, particularly concerning its origin and development. Its diverse clinical presentations can make it challenging to identify, influence its clinical course, and complicate its treatment. It can manifest suddenly with severe symptoms, making it crucial not to disregard it in patients with acute liver failure. Conversely, it can progress slowly, and there's ongoing debate about whether immunosuppressive therapy is necessary in such cases. There are no set time limits for treatment. In recent years, significant advancements have been achieved in the realms of diagnosis, including the introduction of classification criteria and the expansion of therapeutic choices. Early detection, treating unusual presentations, and handling each patient individually are essential for successful management. Unwanted drug side effects are significant in terms of adherence. With the effectiveness of so many new and developing therapeutic alternatives, choosing a course of therapy based on expected side effect profiles may become increasingly crucial and improve patient adherence.

Recommendations include continued investigation into the genetic and environmental factors predisposing individuals to AIH, as well as efforts to identify specific triggers and pathways involved in its development. Additionally, enhanced surveillance and early detection of AIH, particularly in individuals exposed to potential triggers such as certain medications or viral infections, are crucial for timely intervention and improved outcomes. It is necessary to do more heterogeneous collaborative

research to expand our knowledge of AIH and eventually enhance patient outcomes.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Acknowledgments: NA

Conflicts of Interest: None of the authors has conflicts of interest to declare.

Ethical Statement: NA

Author Contribution: All listed authors have contributed significantly to the manuscript

REFERENCES

1. Goel A, Kwo P. Treatment of autoimmune hepatitis. Clinics in Liver Disease. 2024;28(1):51-61.

2. Muratori L, Lohse AW, Lenzi M. Diagnosis and management of autoimmune hepatitis. bmj. 2023;380.

3. Cassim S, Bilodeau M, Vincent C, Lapierre P. Novel immunotherapies for autoimmune hepatitis. Frontiers in Pediatrics. 2017;5:8.

4. El-Sheakh AR, Suddek GM. Celecoxib abrogates concanavalin A-induced hepatitis in mice: Possible involvement of Nrf2/HO-1, JNK signaling pathways and COX-2 expression. International Immunopharmacology. 2023;121:110442.

5. González IA, Hartley CP, Nalbantoglu I. Recurrent Autoimmune Hepatitis and De Novo Autoimmune Hepatitis in the Liver Allograft: Clinical and Histopathologic Characterization. American Journal of Clinical Pathology. 2021;155(3):435-45.

6. Elshal M, Abu-Elsaad N, El-Karef A, Ibrahim T. Etanercept attenuates immune-mediated hepatitis induced by concanavalin A via differential regulation of the key effector cytokines of CD4+ T cells. Life Sciences. 2021;277:119618.

7. Que W, Lin H, Li X, Zhang B, Liu M, Hu X, et al. Koumine ameliorates concanavalin A-induced autoimmune hepatitis in mice: involvement of the Nrf2, NF-κB pathways, and gut microbiota. International Immunopharmacology. 2023;114:109573.

8. Floreani A, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PS, Krawitt E, et al. Etiopathogenesis of autoimmune hepatitis. Journal of autoimmunity. 2018;95:133-43.

9. Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. The Lancet. 2013;382(9902):1433-44.

10. Tamimi TA, Sallam M, Rayyan D, Farah R, Alkhulaifat D, Al-Ani A, et al. Clinical Characteristics of Autoimmune Hepatitis in a Middle Eastern Population: A Tertiary Care Center Experience. Journal of Clinical Medicine. 2023;12(2):629.

11. Sebode M, Hartl J, Vergani D, Lohse AW, Group IAH. Autoimmune hepatitis: From current knowledge and clinical practice to future research agenda. Liver international. 2018;38(1):15-22.

12. Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. Gastroenterology. 2001;120(6):1502-17.

13. Sahebjam F, Vierling JM. Autoimmune hepatitis. Frontiers of medicine. 2015;9:187-219.

14. Ye T, Wang T, Yang X, Fan X, Wen M, Shen Y, et al. Comparison of concanavalin a-induced murine autoimmune hepatitis models. Cellular Physiology and Biochemistry. 2018;46(3):1241-51.

15. Czaja AJ. Transitioning from idiopathic to explainable autoimmune hepatitis. Digestive diseases and sciences. 2015;60(10):2881-900.

16. Tanaka A. Autoimmune hepatitis: 2019 update. Gut and Liver. 2020;14(4):430.

17. Krawitt EL. Autoimmune hepatitis. New England Journal of Medicine. 2006;354(1):54-66.

18. Cai T, Xu L, Xia D, Zhu L, Lin Y, Yu S, et al. Polyguanine alleviated autoimmune hepatitis through regulation of macrophage receptor with collagenous structure and TLR4-TRIF-NF-κB signalling. Journal of Cellular and Molecular Medicine. 2022;26(22):5690-701.

19. Vergani D, Mieli-Vergani G. Aetiopathogenesis of autoimmune hepatitis. World J Gastroenterol. 2008;14(21):3306-12.

20. Ma Y, Su H, Yuksel M, Longhi MS, McPhail MJ, Wang P, et al. Human leukocyte antigen profile predicts severity of autoimmune liver disease in children of European ancestry. Hepatology. 2021;74(4):2032-46.

21. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmmune hepatitis. Cellular & molecular immunology. 2022;19(2):158-76.

22. Lohse AW, Mieli-Vergani G. Autoimmune hepatitis. Journal of hepatology. 2011;55(1):171-82.

23. Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, et al. Autoimmune hepatitis. Nat Rev Dis Primers. 2018;4:18017.

24. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology. 2020;72(2):671-722.

25. Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepatitis research and treatment. 2011;2011.

26. Aljumah AA, Al-Ashgar H, Fallatah H, Albenmousa A. Acute onset autoimmune hepatitis: Clinical presentation and treatment outcomes. Annals of Hepatology. 2019;18(3):439-44.

27. Rahim MN, Miquel R, Heneghan MA. Approach to the patient with acute severe autoimmune hepatitis. JHEP Reports. 2020;2(6):100149.

28. Mendizabal M, Marciano S, Videla MG, Anders M, Zerega A, Balderramo DC, et al. Fulminant presentation of autoimmune hepatitis: clinical features and early predictors of corticosteroid treatment failure. European Journal of Gastroenterology & Hepatology. 2015;27(6):644-8.

29. Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol. 2021;27(1):58-69.

30. Wang H, Feng X, Yan W, Tian D. Regulatory T cells in autoimmune hepatitis: unveiling their roles in mouse models and patients. Frontiers in Immunology. 2020;11:575572.

31. van Gerven NM, de Boer YS, Mulder CJ, van Nieuwkerk CM, Bouma G. Auto immune hepatitis. World journal of gastroenterology. 2016;22(19):4651.

32. Mukherjee D, Bhatt S. Advanced drug delivery systems in hepatocellular carcinoma. Advanced Drug Delivery Systems in the Management of Cancer: Elsevier; 2021. p. 225-34.

33. Aubert V, Graf Pisler I, Spertini F. Improved diagnoses of autoimmune hepatitis using an anti-actin ELISA. Journal of clinical laboratory analysis. 2008;22(5):340-5.

34. Sucher E, Sucher R, Gradistanac T, Brandacher G, Schneeberger S, Berg T. Autoimmune hepatitis—immunologically triggered liver Pathogenesis—diagnostic and therapeutic strategies. Journal of immunology research. 2019;2019.

35. Liu Y, Hao H, Hou T. Concanavalin A-induced autoimmune hepatitis model in mice: Mechanisms and future outlook. Open Life Sciences. 2022;17(1):91-101.

36. Taubert R, Hupa-Breier KL, Jaeckel E, Manns MP. Novel therapeutic targets in autoimmune hepatitis. Journal of autoimmunity. 2018;95:34-46.

37. Liu S-P, Bian Z-H, Zhao Z-B, Wang J, Zhang W, Leung PS, et al. Animal models of autoimmune liver diseases: a comprehensive review. Clinical Reviews in Allergy & Immunology. 2020;58:252-71.

38. Iwamoto S, Kido M, Aoki N, Nishiura H, Maruoka R, Ikeda A, et al. TNF-α is essential in the induction of fatal autoimmune hepatitis in mice through upregulation of hepatic CCL20 expression. Clinical immunology. 2013;146(1):15-25.

39. Liu J, Ma Z, Li H, Li X. Chinese medicine in the treatment of autoimmune hepatitis: Progress and future opportunities. Animal Models and Experimental Medicine. 2022;5(2):95-107.

40. Kusters S, Gantner F, Kunstle G, Tiegs G. Interferon gamma plays a critical role in T cell-dependent liver injury in mice initiated by

concanavalin A. GASTROENTEROLOGY-BALTIMORE THEN PHILADELPHIA-. 1996;111:462-71.

41. Heymann F, Hamesch K, Weiskirchen R, Tacke F. The concanavalin A model of acute hepatitis in mice. Laboratory animals. 2015;49(1_suppl):12-20.

42. Lu Y, Chen J, Ren D, Yang X, Zhao Y. Hepatoprotective effects of phloretin against CCl4-induced liver injury in mice. Food and Agricultural Immunology. 2017;28(2):211-22.

43. Huang H-L, Wang Y-J, Zhang Q-Y, Liu B, Wang F-Y, Li J-J, et al. Hepatoprotective effects of baicalein against CCl4-induced acute liver injury in mice. World journal of gastroenterology: WJG. 2012;18(45):6605.

44. Matsumoto H, Kawamura T, Kobayashi T, Kanda Y, Kawamura H, Abo T. Coincidence of autoantibody production with the activation of natural killer T cells in α-galactosylceramide-mediated hepatic injury. Immunology. 2011;133(1):21-8.

45. Biburger M, Tiegs G. α-Galactosylceramide-induced liver injury in mice is mediated by TNF-α but independent of Kupffer cells. The Journal of Immunology. 2005;175(3):1540-50.

46. Kuriki J, Murakami H, Kakumu S, Sakamoto N, Yokochi T, Nakashima I, et al. Experimental autoimmune hepatitis in mice after immunization with syngeneic liver proteins together with the polysaccharide of Klebsiella pneumoniae. Gastroenterology. 1983;84(3):596-603.

47. Ma X, Jia Y-T, Qiu D-K. Inhibition of p38 mitogen-activated protein kinase attenuates experimental autoimmune hepatitis: involvement of nuclear factor kappa B. World Journal of Gastroenterology: WJG. 2007;13(31):4249.

48. Stine JG, Northup PG. Autoimmune-like drug-induced liver injury: a review and update for the clinician. Expert Opinion on Drug Metabolism & Toxicology. 2016;12(11):1291-301.

49. deLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL, editors. Drug-induced liver injury with autoimmune features. Seminars in liver disease; 2014: Thieme Medical Publishers.

50. Lee W, Denton W. Chronic hepatitis and indolent cirrhosis due to methyldopa: the bottom of the iceberg? Journal of the South Carolina Medical Association (1975). 1989;85(2):75-9.

51. Alshehri MM, Amjad MW, Mudawi MM. Drugs-Inducing Hepatotoxicity. Asian Journal of Pharmaceutical Research and Health Care. 2020:148-56.

52. Dumortier J, Slim R, Chevallier M, Boillot O, Thaunat J, Vaillant E, et al. Acute severe fibrosing hepatitis associated with ciprofibrate treatment. Gastroenterologie clinique et biologique. 1999;23(12):1399-400.

53. Lewis JH. Clinical perspective: statins and the liver—harmful or helpful? Digestive diseases and sciences. 2012;57(7):1754-63.

54. Grewal J, Doan A, Hong AS, Amin A, Scapa JV, Hanna R, et al. Drug-induced autoimmune hepatitis from hydralazine leading to acute liver failure and liver transplantation. ACG Case Reports Journal. 2019;6(10).

55. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135(6):1924-34. e4.

56. Schmeltzer PA. Drug-Induced Liver Injury with Autoimmune Features. Diagnosis and Management of Autoimmune Hepatitis: A Clinical Guide. 2020:151-60.

57. Ramakrishna J, Johnson AR, Banner BF. Long-term minocycline use for acne in healthy adolescents can cause severe autoimmune hepatitis. Journal of clinical gastroenterology. 2009;43(8):787-90.

58. Ghabril M, Bonkovsky HL, Kum C, Davern T, Hayashi PH, Kleiner DE, et al. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. Clinical Gastroenterology and Hepatology. 2013;11(5):558-64. e3.

59. Pape S, Schramm C, Gevers TJ. Clinical management of autoimmune hepatitis. United European gastroenterology journal. 2019;7(9):1156-63.

60. Dyson JK, Wong LL, Bigirumurame T, Hirschfield GM, Kendrick S, Oo YH, et al. Inequity of care provision and outcome disparity in autoimmune hepatitis in the United Kingdom. Alimentary Pharmacology & Therapeutics. 2018;48(9):951-60.

61. Guo J, Shirozu K, Akahoshi T, Mizuta Y, Murata M, Yamaura K. The farnesyltransferase inhibitor tipifarnib protects against autoimmune hepatitis induced by Concanavalin A. Int Immunopharmacol. 2020;83:106462.

62. Ballegeer M, Libert C. Different cell types involved in mediating concanavalin A induced liver injury: a comprehensive overview. J Gastroenterol Hepatology Res. 2016;1(001).

63. Soloway RD, Summerskill W, Baggenstoss AH, Geall MG, Gitnick GL, Elveback LR, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology. 1972;63(5):820-33.

64. Devlin SM, Swain MG, Urbanski SJ, Burak KW. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. Canadian Journal of Gastroenterology and Hepatology. 2004;18:321-6.

65. Bischoff S, Yesmembetov K, Antoni C, Sollors J, Evert M, Ebert M, et al. Autoimmune Hepatitis: a Review of Established and Evolving Treatments. Journal of Gastrointestinal & Liver Diseases. 2020;29(3).

66. Baven-Pronk MA, Hew Jr JM, Biewenga M, Tushuizen ME, van den Berg AP, Bouma G, et al. Calcineurin inhibitors in the treatment of adult autoimmune hepatitis: a systematic review. Journal of clinical and translational hepatology. 2022;10(6):1155.

67. Czaja AJ. Advancing biologic therapy for refractory autoimmune hepatitis. Digestive Diseases and Sciences. 2022;67(11):4979-5005.

68. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene. 2003;22(47):7359-68.

69. Weiler-Normann C, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. Journal of hepatology. 2013;58(3):529-34.

70. Ibrahim KM, Ahmed HI, Ramadan L, Balah A. A low dose of naloxone mitigates autoimmune hepatitis by regulating TLR4/NF-κB and Nrf2/HO-1 signaling pathways. Inflammopharmacology. 2023;31(5):2467-78.

71. Hsu M-C, Liu S-H, Wang C-W, Hu N-Y, Wu ES, Shih Y-C, et al. JKB-122 is effective, alone or in combination with prednisolone in Con A-induced hepatitis. European Journal of Pharmacology. 2017;812:113-20.

72. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193-213.

73. Mieli-Vergani G, Vergani D. Autoimmune hepatitis. Nature Reviews Gastroenterology & Hepatology. 2011;8(6):320-9.

74. Gumm A, Perez-Atayde A, Wehrman A. Posttransplant considerations in autoimmune liver disease: Recurrence of disease and de novo. Clinical Liver Disease. 2022;20(4):130.

75. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011:gut. 2010.235259.

76. Harputluoglu M, Caliskan AR, Akbulut S. Autoimmune hepatitis and liver transplantation: Indications, and recurrent and de novo autoimmune hepatitis. World Journal of Transplantation. 2022;12(3):59.

77. Dumortier J, Chouik Y, Hequet O, Hervieu V, Boillot O. Rituximab and plasmapheresis for severe post-transplant auto-immune hepatitis. Clinics and Research in Hepatology and Gastroenterology. 2021:101844-.

78. Ibáñez-Samaniego L, Salcedo M, Vaquero J, Bañares R. De novo autoimmune hepatitis after liver transplantation: A focus on glutathione S-transferase theta 1. Liver Transplantation. 2017;23(1):75-85.

79. Stirnimann G, Ebadi M, Czaja AJ, Montano-Loza AJ. Recurrent and de novo autoimmune hepatitis. Liver transplantation. 2019;25(1):152-66.

80. Aguilera I, Wichmann I, Sousa J, Bernardos A, Franco E, Garcia-Lozano J, et al. Antibodies against glutathione S-transferase T1 (GSTT1) in patients with de novo immune hepatitis following liver transplantation. Clinical & Experimental Immunology. 2001;126(3):535-9.

81. Guido M, Burra P, editors. De novo autoimmune hepatitis after liver transplantation. Seminars in liver disease; 2011: © Thieme Medical Publishers.