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Review

Autoimmune Hepatitis Management: Recent Advances and Future Prospects

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Abstract: Autoimmune hepatitis (AIH) is a varied inflammatory chronic liver disease. AIH's prevalence varies and has increased recently. Diagnosis involves the discovery of histologic features following liver biopsy and serologic testing. Clinical features vary, and up to 40% of patients may be asymptomatic. Evaluating thiopurine methyltransferase (TMPM) activity before treatment is crucial for an optimal response. The primary treatment goal is biochemical remission, normalized serum IgG, and liver enzymes. Induction therapy typically involves azathioprine and corticosteroids. Close monitoring of liver function tests and serum immunoglobulin levels is essential. Medications can be tapered after achieving biochemical remission. Liver transplantation may be required for refractory disease or cirrhosis. Further therapeutic approaches are needed, particularly for non-responders to first-line treatments.

Keywords: autoimmune hepatitis; immunosuppressive agents; biochemical remission; induction therapy; non-responder management

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1. Introduction

Autoimmune hepatitis (AIH) is an inflammatory chronic liver disease with an unknown etiology, exhibiting diverse presentations, including acute liver failure and potential progression to cirrhosis. Initially observed in young females, it was characterized by elevated serum immunoglobulins, mainly IgG, and showed positive responses to steroid precursors [1]. In the late 1900s, AIH emerged as the pioneering form of chronic liver disease, demonstrating improved patient survival with medical therapy involving corticosteroids alone or combined with the immunomodulator azathioprine during the early active phase of the disease [2].

Recent times have witnessed notable fluctuations in AIH incidence and prevalence, ranging from 0.4 to 2.39 per 100,000 for incidence and 4.8 to 42.9 per 100,000 for prevalence [3]. These variations might be attributed to diagnostic challenges, particularly in resource-limited regions, where confirmation often relies on objective and clinical data utilizing scoring systems proposed by the International AIH Group (IAIHG) [4]. Recognizing the limitations of these tools, ongoing research endeavors to develop more reliable diagnostic approaches.

The primary treatment approach remains corticoid induction therapy, followed by maintenance with a combination of steroids and azathioprine [5]. In cases of first-line therapy failure, alternative immunosuppressants can be considered second-line treatment. The

ultimate therapeutic goal is achieving biochemical remission, characterized by normal liver transaminases and immunoglobin G levels [5]. Treatment regimens must be individualized to achieve optimal outcomes, with diligent monitoring of potential side effects.

This review aims to provide the latest updates on the proposed disease pathogenesis, ongoing research on diagnostic biomarkers, and the current and investigational treatment options available for AIH.

2. Clinical Features

Most patients are typically in their second or fifth/sixth decade, with around three-quarters of AIH patients being women [6]. Among elderly patients, autoimmune hepatitis exhibits typical serological and genetic traits and patients are often asymptomatic. However, the prognosis and treatment response of these patients are comparable to younger patients [7]. Given the diverse natural course of autoimmune hepatitis, it manifests clinically in the following three main patterns: asymptomatic, insidious onset, and acute onset.

The initial diagnosis may uncover that up to 40% of AIH patients are asymptomatic, but the majority eventually develop symptoms throughout the disease [1,8]. Asymptomatic patients do not exhibit liver-related signs or symptoms. They are typically evaluated when abnormal liver function tests are incidentally discovered or when investigating other medical conditions, particularly extra-hepatic autoimmune disorders.

Insidious onset may present with non-specific symptoms like fatigue, anorexia, abdominal pain, nausea, and arthralgias [7].

The acute onset of autoimmune hepatitis has become increasingly common worldwide, affecting not only adults but also children and adolescents [9]. Approximately 25% of AIH patients form a subset that displays severe acute liver injury [9], characterized by jaundice, coagulopathy, and notable liver enzyme elevations, ranging from five to ten times the upper limit of the normal range [10]. The diagnosis is supported by elevated levels of IgG, along with the presence of characteristic autoantibodies such as antinuclear antibodies, smooth muscle antibodies (SMAs), liver/kidney microsomal antibody type 1 (anti-LKM1), liver cytosol antibody type 1 (anti-LC1), and soluble liver antigen/liver pancreas antibodies (anti-SLA/LP) [11,12].

Another presentation is acute-on-chronic liver failure, which occurs when an autoimmune hepatitis flare arises in patients previously diagnosed with or undiagnosed chronic liver disease (AIH-ACLF). The ACLF Consortium of the Asian Pacific Association for the Study of Liver defines ACLF as individuals exhibiting jaundice (bilirubin > 5 mg/dL) and coagulopathy (PT [INR] $\geq$ 1.5), complicated by ascites and/or encephalopathy within 4 weeks after diagnosis [13]. AIH is frequently overlooked as a cause of ACLF, necessitating a high index of suspicion for its diagnosis [14]. The presentation of AIH-ACLF is often unusual, with nearly half of the patients being seronegative. Thus, a liver biopsy with a lower threshold may be required to establish the diagnosis [14].

3. Diagnosis

There is no single specific biomarker for AIH diagnosis. Traditional serum biomarkers of liver injury and treatment response in AIH include aminotransferases (AST and ALT), IgG, and, less frequently, 6-thioguanine (6-TG). While liver biopsies are specific to the active disease upon initial presentation, their impracticality for serial use, particularly in decisions regarding immunosuppressive therapy (IST) optimization, poses challenges. Consequently, there is a pressing demand for noninvasive blood-based biomarkers that can accurately identify patients at a heightened risk of relapse or function as early indicators of relapse [15].

Novel candidate noninvasive biomarkers are emerging from gene expression profiles, proteins, metabolites, and immune cell phenotypes observed at various stages of the disease. Growth Differentiation Factor 15 (GDF15) has garnered attention as a potential diagnostic and therapeutic marker for AIH. Arinaga-Hino et al. conducted a clinical trial involving 45 patients to explore GDF15's potential in Japan. Their findings revealed

significantly elevated serum GDF15 levels in AIH patients, particularly those without cirrhosis, compared to individuals with other liver diseases. The study demonstrated promising diagnostic accuracy, with a sensitivity of 95.6% and a specificity of 60.9%, in distinguishing AIH from other liver conditions. Furthermore, treatment-induced remission was associated with a noticeable decrease in serum GDF15 levels, suggesting its utility in assessing treatment response. However, excluding patients with various comorbidities, such as cancer and cardiovascular disease, prompts further investigation to ascertain the generalizability of these findings and explore GDF15's prognostic value and its potential to differentiate atypical forms of AIH from other liver conditions [16].

To better understand the evolving diagnostic landscape in autoimmune hepatitis (AIH) management, we present a concise summary of Table 1 featuring emerging noninvasive biomarkers. This table highlights novel inflammatory markers and other promising candidates currently under investigation for their potential diagnostic and therapeutic roles in AIH [15].

Table 1. Novel inflammatory markers for the diagnosis and management of autoimmune hepatitis [15].

Biomarker	Description
ADA	Adenosine deaminase, a potentially useful marker for assessing disease activity and treatment response in autoimmune hepatitis.
M65 Cytokeratin-18	A marker of cell death that may reflect liver injury in autoimmune hepatitis.
TGF-ß1	Transforming Growth Factor beta-1, involved in hepatic fibrosis in autoimmune hepatitis.
BAFF	B-cell Activating Factor, associated with disease progression in autoimmune hepatitis.
Anti-ASGPR	Autoantibodies against the asialoglycoprotein receptor, potentially useful for the diagnosis of autoimmune hepatitis.
FOXP3/RORɣt Ratio	The ratio between the transcription factors FOXP3 and RORγt, which may serve as markers of disease activity in autoimmune hepatitis.
DNase 1	An enzyme that may be involved in the pathogenesis of autoimmune hepatitis.
Ferritin	A marker of inflammation and oxidative stress in autoimmune hepatitis.
CD74: MIF Ratio	The ratio between CD74 and Macrophage Migration Inhibitory Factor (MIF), potentially relevant in the pathogenesis of autoimmune hepatitis.
Vitamin D Receptor	Involved in immune regulation and may be a therapeutic target in

The process poses a clinical challenge, as diagnostic criteria rely on scoring systems developed by national societies. The original and revised scoring systems, created in 1993 and 1999, respectively, have been replaced by a simplified scoring system, which is widely utilized in clinical practice.

4. The Original and Revised Scoring Systems

The original scoring system, the first standardized system for AIH, initially aimed to recruit prospective AIH research trials rather than diagnosing AIH. Although it was a pioneering tool for guiding AIH diagnosis, it had a significant drawback in its lack of specificity, particularly in distinguishing AIH from other cholestatic liver diseases [10]. Notably, this initial scoring system considered other less common but significant autoantibodies for AIH diagnosis, such as p-ANCA, anti-SLA, anti-LP, HLA DR3, DR4, and the impact of

treatment response or relapse. Subsequently, a revised scoring system emerged to address the differentiation issue between AIH and cholestatic diseases, primarily by incorporating new autoantibodies and modifying some parameter scores.

However, both scoring tools were deemed impractical due to their sole reliance on expert consensus and the inclusion of numerous criteria. To address this, a simplified scoring system was introduced in 2008, showing promising clinical outcomes. Nonetheless, the revised scoring system is still utilized to evaluate atypical disease features or when AIH diagnosis remains uncertain [17].

5. Simplified Scoring System

This clinical instrument was specifically designed for diagnosing AIH, in contrast to the first two scoring systems used primarily for research purposes. The development of this tool involved studying 359 patients, while the revised and original versions relied on expert consensus. The primary aim was to create a user-friendly bedside tool that performed as effectively as the original and revised scoring systems. Its key strengths include high diagnostic specificity for AIH and the ability to rule out overlaps or diagnostic uncertainties accurately [18].

The scoring system comprises the following four major components: specific antibodies, serum IgG level, liver histologic features, and the presence of viral hepatitis. Each element contributes a maximum of two points to the total score. Scoring six points indicates probable disease, while seven or more indicates a definite diagnosis [17,18]. ANA or SMA antibodies yield one point with a cutoff of >1:40 and two points with >1:80. The LKM-1 Antibody scores two points (>1:40), and any SLA antibody titer adds two points each. IgG levels above the upper limit but <1.10 times the normal score one point, and $\geq$1.10 times score two points. Liver histology compatible with AIH adds two points, characterized by lymphoplasmacytic infiltration, portal inflammation, interface hepatitis, rosettes, or emperipolesis; liver histology typical of AIH (one point) lacks cellular infiltration and inflammation. The absence of viral hepatitis contributes two points. The maximum score in the simplified scoring system is eight points [18].

Diverse studies have validated the score's performance across diverse populations [19,20]. For instance, Qiu et al. compared it with the original revised criteria, finding comparable sensitivity and specificity in diagnosing AIH among Chinese patients [20]. Specifically, they reported 90% sensitivity and 95% specificity for probable AIH and 62% sensitivity and 99% specificity for definite AIH [20]. Similarly, in a study conducted on Italian AIH patients, high sensitivity and specificity were found for the simplified score, revealing that 91.8% of patients reached a score of 6, while 87.1% reached a score of 7, highlighting the reliability of the simplified criteria in identifying AIH cases [19]. Studies suggest that the simplified score is easy to apply and offers high sensitivity and specificity, particularly with a score of 7, which enhances specificity without compromising sensitivity [19,20].

Some factors currently not included in the scoring system are the use of ANA immunofluorescence on tissue sections of HEp2 cells, corresponding to an immortalized cell line mostly used in vitro for the detection of autoimmune diseases. This has shown to be a reasonable option for ANA evaluation in AIH when the cutoff titer is increased to an interval between 1:160 and 1:320. Accordingly, it has been reported that F-Actin ELISA for ANA evaluation could be an equivalent alternative to ANA IFT and could be added to the simplified scoring system [18]. Nonetheless, it has been shown that the ELISA assay for detecting F-actin antibodies exhibited satisfactory specificity only when employed at a modified (higher) cut-off value [18]. So, utilizing ELISA for detecting anti-actin antibodies may be beneficial when there are uncertainties in the interpretation of standard indirect immunofluorescence, enhancing the diagnosis of autoimmune hepatitis (AIH) [21].

Non-organ specific autoantibodies (NOSAs) are commonly found in HCV-positive individuals, with SMA being the most prevalent, followed by ANA, and less frequently, LKM1. However, the immunofluorescent patterns of SMA and ANA detected on tissue sections differ from those typically observed in autoimmune hepatitis (AIH) [22,23]. In AIH,

SMA displays the actin pattern, staining arterial vessels (V), renal glomeruli (G), and tubules (T), whereas in HCV infection, it usually exhibits the V pattern. ANA, which usually shows a homogeneous pattern in AIH, tends to display a speckled pattern in HCV infection [22,23]. Studies have shown that the development of non-organ-specific autoantibodies seems to be closely linked to the genetic background predisposing individuals to AIH. Specifically, HLA A1-B8-DRB10301 and DRB10401 have been associated with the emergence of antinuclear antibodies and autoimmune conditions such as autoimmune thyroiditis, synovitis, and vasculitis in North American and Chinese patients with chronic viral hepatitis [22,23]. Similar to findings in AIH and primary biliary cirrhosis (PBC), HLA-DRB1*11 is believed to be protective against the development of autoreactivity in HCV-infected individuals [22]. Therefore, and since both entities can co-exist, it is essential to include in the diagnostic workup of AIH an autoantibody assessment to rule out other causes that can trigger autoantibody production, in order to avoid a misleading diagnosis [23].

The guidelines from the American Association for the Study of Liver Diseases (AASLD) outline three essential parameters for comparing the revised and simplified scoring systems [24]. In comparison to the simplified version, the revised scoring system shows higher sensitivity (100% vs. 95%), lower specificity (73% vs. 90%), and reduced accuracy (92% vs. 82%). As a result, these tools cannot be used interchangeably. The revised version is deemed to hold greater diagnostic value in patients with atypical features of AIH, and it is suggested that relying solely on the simplified version may lead to delayed diagnosis in such cases [25].

6. Proposed Pathogenesis

The current pathogenesis of AIH is believed to initiate with the presence of autoantigenic peptides, which are detected by dendritic cells. This antigenic exposure, along with costimulatory signals, leads to the maturation of naïve TCD4+ cells into different T helper cells based on the cytokine stimuli they receive. Notably, IL-12 triggers the activation of NK cells, predominantly found in the liver parenchyma, impacting fibrogenesis, tumorigenesis, and promoting liver inflammation and tissue damage [25,26]. Furthermore, IL-4 induces the formation of Th2, while TGF-ß serves a similar function for Treg and Th17 cell differentiation from naïve Th0 cells in the presence of IL-12.

The crucial role of Treg and Th17 in AIH development must be emphasized. T regulatory cells, comprising CD8+ and CD4+/CD25+ cells, are significantly affected in AIH, with diminished Treg cells and notably reduced FOXP3 levels in both peripheral and liver tissue samples [26] (Figure 1). These Treg cells are vital for autoimmune homeostasis, and their reduced inhibitory effect leads to an imbalance among immune cells and cytokine levels. Consequently, there is an increase in Th17/Th22 levels, resulting in elevated cytokine production of IL-22, IL-13, IL-17, Interferon-γ, and granzyme B16 [27]. Specifically, IL-17 promotes inflammatory cytokines such as IL-6 and TNF-α, further perpetuating the autoimmune response [26,27].

Hence, the imbalance between T regulatory cells and its FOXP3 compared to Th1 and Th17/Th22 is the primary proposed autoimmune dysfunction in AIH [27]. This imbalance triggers a cytokine disbalance, leading to overactivation of NK cells, macrophages, and complements, resulting in hepatic inflammation and subsequent fibrosis observed in AIH. These critical factors are targeted by current treatments and may be influenced by the genetic predisposition and environmental factors of the subjects [28].

Variations in genes encoding human leukocyte antigens (HLAs) play a significant role in AIH pathogenesis and onset [28–30]. Amidst autoimmune hepatitis type 1 (AIH-1), predisposition is notably linked to the presence of the MHC class II HLA allele DRB103:01, which is associated with earlier disease onset and a more severe clinical course [30]. In populations where DRB103:01 is scarce, such as in Asia, susceptibility to AIH-1 is conferred by the DRB104 allele, which is associated with later disease onset and a milder disease presentation [30]. Conversely, autoimmune hepatitis type 2 (AIH-2) is associated with the presence of the DRB1*07 allele. In addition, DRB1*13 is associated with histologi-

cally more advanced disease, while DRB1*07 is linked to the least optimal response to immunosuppressive therapy [30].

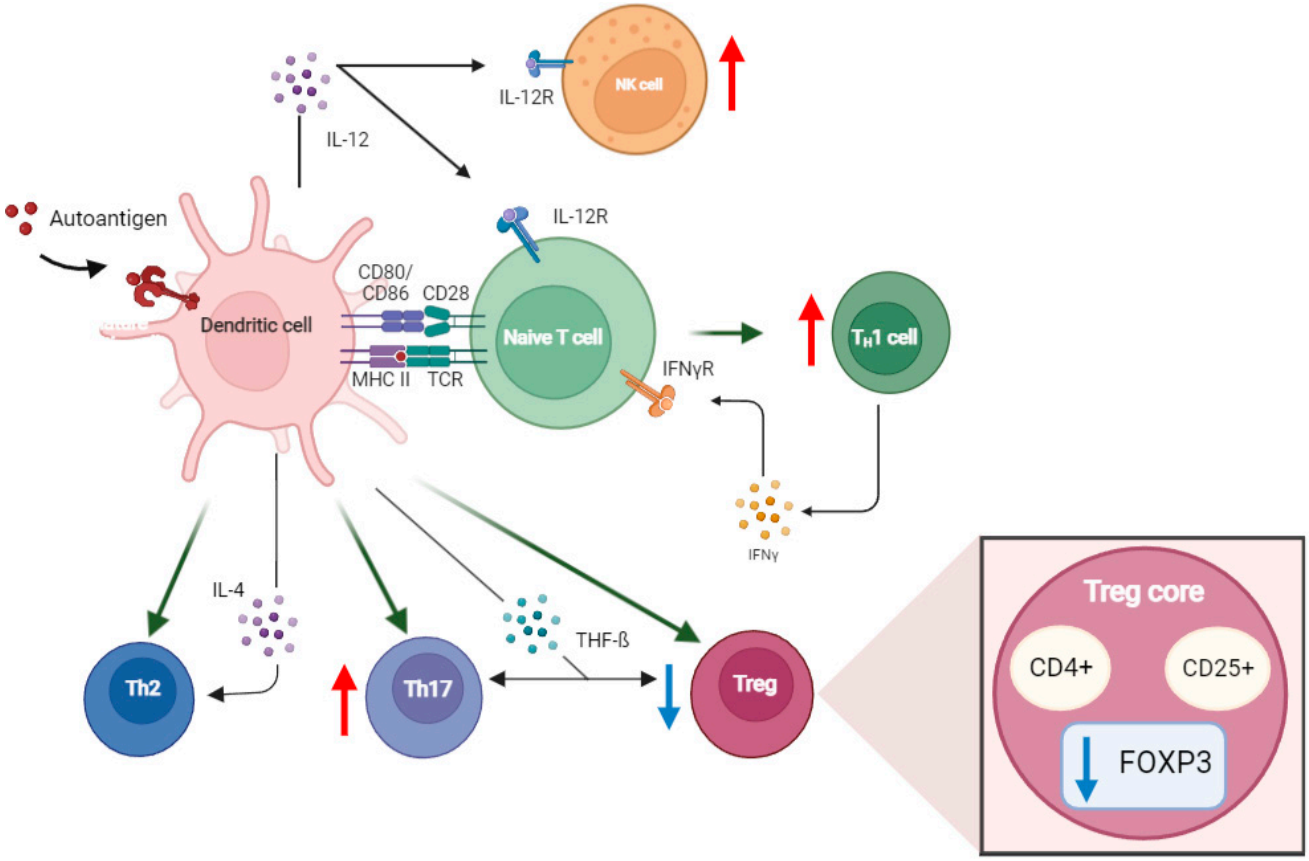

Figure 1. AIH pathogenesis. Arrays highlighted in blue descending vertically, denote a decrease, while those in red ascending vertically, indicate an increase.

AIH can be further classified according to serology into AIH type 1 and AIH type 2. AIH-1 is characterized by positive ANAs and or anti-smooth muscle antibodies (SMAs) [31]. Meanwhile, AIH-2 is usually characterized by positive anti-liver kidney microsomal antibody type one (LKM1) and anti-LKM3 and/or anti-liver cytosol type one antibody (LC1) [32]. Furthermore, up to 20% of AIH cases have negative serology for ANA, SMA, and LKM1 autoantibodies, despite the presence of other characteristic features of AIH [32].

The ongoing immune-mediated inflammation can result in progressive destruction of liver cells and tissue. If untreated, ongoing damage can lead to histological changes in the liver, including interface hepatitis, portal inflammation, and bridging fibrosis [32]. These changes can lead to cirrhosis in a subset of patients, which ultimately leads to liver dysfunction, portal hypertension, ascites, hepatic encephalopathy, and an increased risk for hepatocellular carcinoma (HCC) [33].

Untreated acute autoimmune hepatitis does not necessarily lead to immediate liver failure, but most patients will experience a spontaneous partial recovery and sometimes even show normal lab values. Nevertheless, histological disease activity usually progresses, and another case of exacerbation is typically anticipated [33].

7. Disease Management

The majority of newly diagnosed AIH patients require treatment. Indications for treatment encompass elevated levels of liver enzymes, active disease based on liver biopsy histology, cirrhosis with evidence of inflammation, or liver enzyme levels greater than twice the upper limit of normal, along with any symptoms or hyperbilirubinemia [34].

The goal of initiating treatment is to induce remission, as defined by (1) the normalization of liver enzymes, including aminotransferases and bilirubin, (2) normalization of serum gamma globulin levels, (3) resolution of clinical symptoms, and (4) improvement in histological inflammation on liver biopsy [5].

Research has shown that AIH patients show better outcomes with immunosuppressive therapy as a first-line treatment, either by using corticosteroids exclusively or combination therapy of a low corticosteroid dose along with azathioprine [35]. According to the 2019 AASLD guidelines, prednisone is given either as a standalone treatment daily with a dose of 40–60 mg in adults or at a lower dose of 20–40 mg if given with AZA. Also, some medical centers recommend initiating prednisone at 1 mg/kg for adult patients and subsequently reducing the dosage once a positive response is observed. Meanwhile, the 2015 European Association for the study of Liver (EASL) guidelines advocates 0.5–1 mg/kg/day prednisone as the initial treatment, followed by 50 mg/day AZA [36].

After four to eight weeks, if there is evidence of a positive biochemical response with improved liver function tests and gamma globulin levels, a gradual steroid reduction can be initiated. Upon achieving remission, steroid withdrawal can be attempted. If remission persists for 12–24 months after steroid withdrawal, tapering and discontinuation of AZA, if used, can be considered. However, treatment responses are variable among AIH patients. Some have an early response as soon as seven to fourteen days after initiating treatment, while others have a delayed response even at eight weeks [37,38]. AIH patients who achieve a response have a comparable survival rate to the general population. The longer remission is maintained, the more favorable overall survival they will have [38]. Figure 2 provides an overview of the initial management of AIH.

A minority of patients experience treatment failure or an incomplete response (approximately 8% and 15% of those undergoing treatment, respectively) and may require second-line options. Intolerance to azathioprine typically appears early in treatment and patients should undergo a trial of re-exposure at a lower dose, preferably with 6-mercaptopurine, which is tolerated by up to 50% of azathioprine intolerant patients [39]. If both azathioprine and 6-mercaptopurine are intolerable, mycophenolate mofetil is the preferred second-line therapy at a standard dose of 2 g/day [40]. However, mycophenolate mofetil may also be ineffective; adjustments to standard therapy, potentially including the addition of allopurinol, should be considered based on measured 6-thioguanine concentrations. If these measures fail, third-line therapies are warranted. Other options may include biologic agents, alternative calcineurin inhibitors like cyclosporine, and anti-neoplastic agents such as methotrexate and cyclophosphamide [40]. Second- or third-line treatment can vary between providers and centers, especially in those where liver transplants are available. Despite the published guidelines, this evidence shows the need for more high-quality evidence [41].

Recently, biological agents have shown promising results in refractory AIH [42]. As autoimmune-associated B cells have a significant role in AIH and BAFF levels are usually high [43], belimumab is a monoclonal antibody that works against the B cell activating factor and has shown significant results in several patients who did not improve with other lines of treatment [44].

Budesonide, a synthetic steroid, has been shown to induce less systemic side effects when compared with other agents, due to its high first-pass hepatic clearance rate. While budesonide was less effective than prednisone when used as the primary medication, it was linked to a reduced incidence of side effects [45]. However, budesonide is contraindicated in cirrhotic patients because portosystemic shunting may reduce the drug's efficacy. In practice, budesonide is infrequently chosen as the initial treatment and is typically reserved for patients with less severe disease and low baseline transaminases [46].

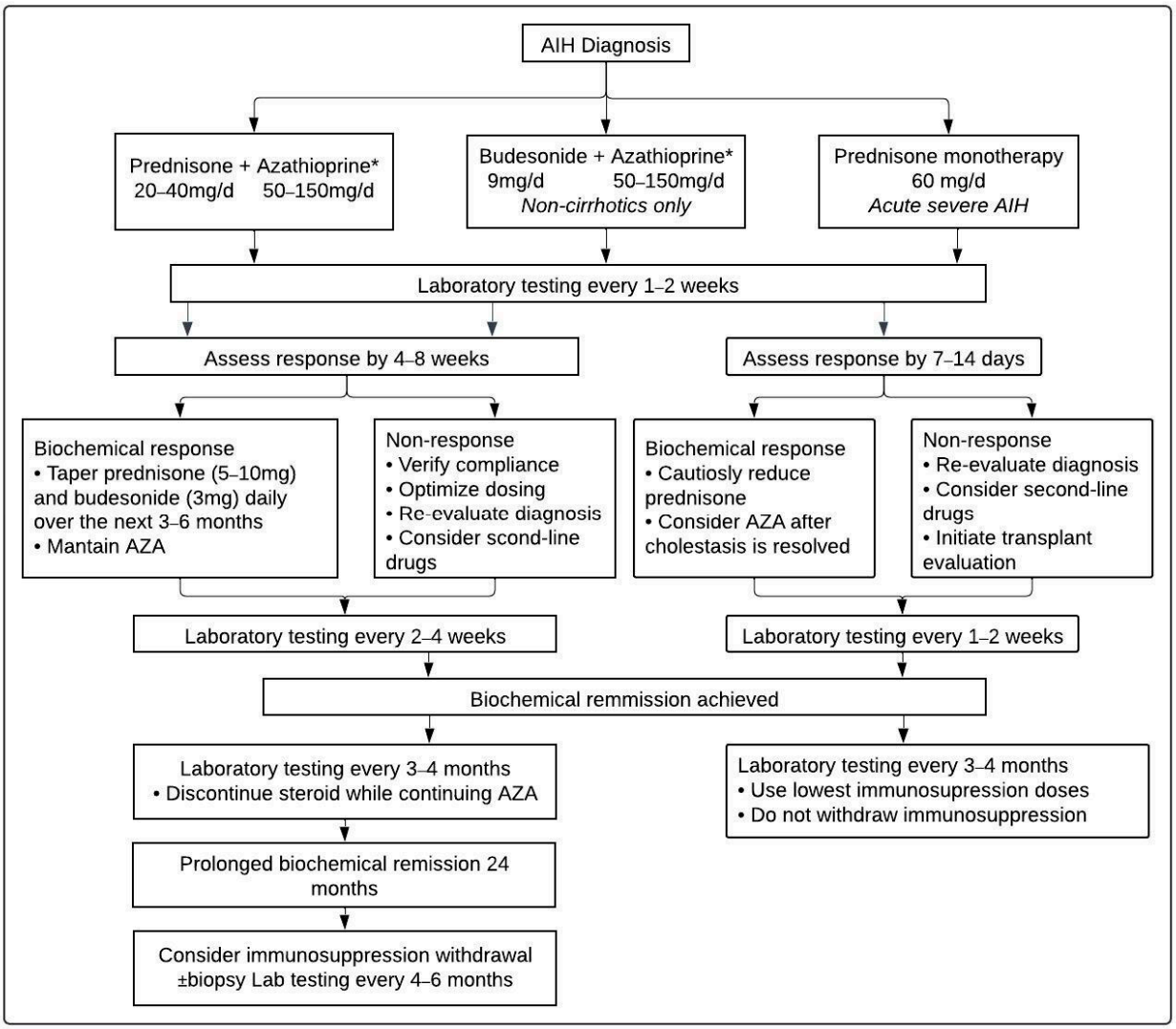

Figure 2. First-line treatment of AIH. AIH: autoimmune hepatitis; AZA: azathioprine. * To achieve an optimal response, pre-treatment testing of thiopurine methyltransferase is necessary.

It will be important to consider that for patients reaching AIH end-stage chronic liver disease, the AASLD guidelines recommend semi-annual ultrasounds for HCC detection for patients with compensated AIH liver cirrhosis, similar to any other cause of liver cirrhosis [5]. Alpha-fetoprotein has also been widely used for HCC surveillance but has limited sensitivity and specificity [45]. More specific recommendations for early HCC detection in AIH cirrhosis are still being debated [5,47].

8. Mechanism of Action of Proposed Therapies

8.1. Glucocorticoids

Glucocorticoids act upon glucocorticoid receptors, and responsive genes and are involved in the process of release of anti-inflammatory molecules. It is well established that the first line of therapy for AIH is generally prednisone alone or in combination with AZA. Prednisone, in the liver, is transformed into prednisolone, which in its unbound form is the active metabolite that produces the therapeutic effect by diffusing through the cell membrane to bind the glucocorticoid receptor (GR). Once the prednisolone–GR complex is activated, the complex translocates to the nucleus to bind the positive or negative GR-responsive elements (GREs) in the promoter regions of the genes to increase or decrease the gene expression [48].

When the binding occurs in the negative GRE, the transcription of inflammatory genes that produce interleukins 1β, IL-2,IL-4,IL-5, IL-6, IL-12,TNF-α and INF-γ is suppressed. Another therapeutic pathway in the action of glucocorticoids is to antagonize the activity of transcription factors required for cytokine transcription like Nuclear Factor Kappa B (NF-kB), activated protein-1 (AP-1) complex and nuclear factor of activated T cells (NF-AT) [48].

On the other hand, when positive GRE is induced, it promotes the transcription of immunosuppressive genes like annexin-1, mitogen-activated protein kinase (MAPK), IL-1 receptor antagonist, and IL-10, which counteract the effect of pro-inflammatory cytokines IL-1. Glucocorticoids also induce the transcription of the gene-encoding inhibitor of Nuclear Factor Kappa B subtype a (IkBa), which downregulates pro-inflammatory cytokines secretion. Recent findings suggest that glucocorticoids play a role in promoting remission by increasing the number and function of regulatory T cells specifically the CD4+CD25+ subset. These Tregs help suppress cell-mediated cytotoxic responses, potentially contributing to the resolution of inflammatory conditions or autoimmune diseases [48].

8.2. Azathioprine

Azathioprine (AZA) is a purine analogue that acts as an antagonist to the endogenous purines that provoke a cytotoxic effect by being metabolized to thiopurine nucleotides. AZA undergoes liver metabolism and it is transformed to 6-mercaptopurine (6-MP) and methyl nitroimidazole. In the intracellular space, 6-MP becomes further transformed into three different enzymes, 6-thiouric acid (6-TU), 6-methyl-MP (6-MMP), and 6-TG nucleotides (6-TGN). 6-TGN is incorporated in the DNA of the leukocyte and promotes cell-cycle arrest and apoptosis. Another mechanism of 6-TGN generating immunosuppression is carried out by one of its phosphorylated forms, 6-thioguanine triphosphate (6-TGTP), which inhibits Rac1 by co-stimulation of CD28, inducing T-cell apoptosis. G-TGTP binding to Rac1 suppresses the activation of Rac1 target genes leading to apoptosis by the mitochondrial pathway [48].

9. Pretreatment Evaluation

Thiopurine methyltransferase (TPMT) metabolized 6-MP into inactive metabolites; therefore, in order to minimize treatment-associated complications and achieve an optimal response, pre-treatment testing is crucial for AIH patients. Before starting AZA, patients should undergo TMPM activity testing. Given that variation in TPMT can increase the available 6-MP, this can be converted to 6-TGN, enhancing the toxic effects. Individuals with low or absent activity are at risk of severe myelosuppression when treated with AZA, necessitating consideration of alternative agents [5,48].

10. Experimental Therapies

10.1. Anti-Tumor Necrosis Factor Therapy

Tumor necrosis factor alpha (TNFα) plays a crucial role in inflammatory liver diseases, and emerging research increasingly links it to the development of AIH. In AIH, T cells that produce TNFα, IFNγ, and IL17 are thought to initiate or contribute to liver damage. Studies have shown that lymphocytes infiltrating the liver in AIH are enriched with these cytokine-secreting T cell populations. While infliximab has been utilized as a salvage treatment in select cases of challenging AIH, initial reports suggest it can alleviate inflammation. However, caution was warranted due to the high incidence of infectious complications associated with its use [46].

10.2. B Cell-Activating Factor of the Tumor Necrosis Factor Family (BAFF)

Currently, there have been no formal trials examining the potential of targeting the BAFF pathway in treating AIH. However, there is an ongoing study called AMBER, which consists of the following two parts: a randomized, double-blind, placebo-controlled multi-center trial. The study aims to assess the safety and effectiveness of VAY736 (ianilumab) in AIH patients who have not adequately responded to standard therapy or cannot tolerate

it. The primary objectives of the study include evaluating whether VAY736 can effectively treat AIH patients who do not respond to or cannot tolerate standard therapy, determining the safety profile of VAY736 in AIH patients, identifying the optimal dosage of VAY736, and assessing whether combining VAY736 with standard treatment yields superior outcomes compared to standard treatment alone (ClinicalTrials.gov: NCT03217422).

10.3. JKB-122

JKB-122, developed by Taiwan J Pharmaceuticals Co., Ltd. (Zhubei City, Hsinchu County 302058, Taiwan), functions as a TLR4 antagonist and possesses hepatoprotective and anti-inflammatory properties. In a Phase 2 pilot study, participants diagnosed with autoimmune hepatitis (AIH) and exhibiting liver enzyme levels ranging from 1.25 to 10 times the upper limit of normal (ULN) received JKB-122 once daily for 24 weeks. This trial targeted individuals who had experienced treatment failure, incomplete response, intolerance, ineligibility, or unwillingness to undergo current immunosuppressive therapies (ClinicalTrials.gov (NCT02556372)).

10.4. Future Therapies

New investigations aim to explore safer and more specific therapeutic candidates such as Garcinone E (GE) against concanavalin-A (Con-A)-induced hepatitis. Con-A is a widely employed model to induce AIH in mice that closely mimics the features of human AIH, with a high affinity for mannose-rich glycoproteins on liver sinusoidal endothelial cells, and triggers T cell activation, particularly CD4+ T cells, leading to the secretion of pro-inflammatory cytokines such as TNF-α, ILs, and IFN-γ, which drive inflammation and cell communication [6]. The results indicate that pretreatment with GE significantly reduces serum markers (transaminases, ALP, LDH, and γ-GT) and histopathological liver lesions induced by Con-A. GE demonstrates potent hepatoprotective effects, possibly attributed to its anti-inflammatory, antioxidant, and anti-apoptotic properties, which modulate HO-1/Nrf2 signaling and suppress the NF-κB-mediated inflammatory cascade and TNF-α/JNK-induced apoptosis pathway. These findings highlight GE as a promising novel candidate for the treatment of AIH [49].

11. Liver Transplantation

Despite advancements in AIH treatment, approximately 10–20% of patients progress to end-stage liver disease and eventually require LT [1]. AIH accounts for 5% of all LT procedures performed in the United States [49]. Patient and graft survival rates at 5 years are 76% and 70.9%, respectively [50,51]. Although these rates are satisfactory, there is a relatively higher risk of late acute rejection (9%), chronic rejection (16%), and recurrent disease (36% to 68% at five years) compared to other LT indications [51].

Post-LT, determining the appropriate candidates for immunosuppressive maintenance therapy is crucial in the management of AIH [52,53]. Immunosuppressive protocols aim to strike a balance between the long-term morbidity and mortality risks in AIH patients following LT. The 2019 AASLD guidelines advocate for a gradual withdrawal of steroids, which has been shown to enhance the metabolic profile (reducing the incidence of hypertension, hyperlipidemia, and diabetes mellitus) without increasing the risk of liver graft failure [5].

12. Metabolic Syndrome

Metabolic syndrome, characterized by a cluster of medical comorbidities such as obesity, hyperlipidemia, hypertension, and insulin resistance, poses a higher risk of cardiovascular disease for affected individuals [26]. Prolonged corticosteroid therapy in AIH patients may increase the risk of developing metabolic syndrome, which in turn is associated with a higher risk of cardiovascular disease-related mortality. Moreover, AIH patients with metabolic syndrome are less likely to achieve biochemical remission within 3 years after diagnosis. Managing metabolic syndrome involves lifestyle modifications, address-

ing individual components, and minimizing glucocorticoid usage whenever possible [5]. Identifying AIH patients at greater risk for metabolic syndrome enables personalized management to mitigate its long-term consequences in this population.

13. Conclusions

Accurate and timely diagnosis, along with effective management, are crucial in improving AIH symptoms and achieving biochemical remission, potentially reducing the risk of disease progression and the need for a liver transplant. Induction therapy involves a combination of prednisone or budesonide and AZA. Prior to initiating AZA, assessing TMPM activity is essential. Regular monitoring of treatment response is advised, and immunosuppression may be tapered in those with sustained biochemical improvement. Post-LT patients should maintain low-dose immunosuppression, with corticosteroids withdrawn as tolerated. Second-line therapies exist for cases of treatment failure, non-response, or drug intolerance. Prospective, multicenter studies focusing on second-line treatments would aid in defining optimal options for refractory patients. Addressing metabolic syndrome is important, as it can negatively impact the quality of life in AIH patients.

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