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REVIEW

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# Autoimmune hepatitis: Current and future therapies

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**Abstract**

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can lead to cirrhosis and liver failure. AIH can present in all ages, races, and ethnicities, but it predominantly affects women. As a heterogeneous disease, AIH presents variably in different patients, making diagnosis and treatment a challenge. Currently, the standard treatment for AIH comprises immunosuppressants; however, their long-term use is associated with adverse effects. The pathogenesis of AIH is complex, involving T cells, macrophages, and plasma cells that invade the periportal parenchyma and lead to an inflammatory cascade that can result in liver damage. Due to the complexity of AIH pathogenesis, treatment targets several inflammatory pathways. However, unlike other autoimmune diseases in which targeted treatments have been approved, there has been little progress made in advancing the treatment paradigm for AIH. Major obstacles to progress include challenges in conducting clinical trials, particularly patient recruitment and ensuring a diverse range of backgrounds; poorly defined outcomes to assess treatment response and improved quality of life; and a lack of study designs that account for the stage of disease and variations in treatment. A focus on individualized and steroid-free treatment approaches is needed to improve AIH prognosis and minimize steroid-associated adverse effects.

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can lead to cirrhosis and liver failure if left uncontrolled.[1] AIH can affect all ages, races, and ethnicities. Both genders are affected; however, AIH is predominantly observed in females (60%–76% of children [< 18 y] and 71%–95% of adults).[2] The worldwide annual incidence and prevalence of AIH stands at 1.37 and 17.44 per 100,000 people, respectively.[3,4] In the United States, the prevalence of AIH is 26.6 per 100,000 people.[5] Notably, AIH is more prevalent in European and American populations than in Asian populations.[3,6] Further, people of

**Abbreviations**: ADCC, antibody-dependent cellular cytotoxicity; AIH, autoimmune hepatitis; BAFF-R, B-cell activating factor receptor; MASLD, metabolic dysfunction–associated steatotic liver disease; MMF, mycophenolate mofetil; MSC, mesenchymal stem/stromal cell; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; PBC, primary biliary cirrhosis; PC, plasma cell; TGFβ, transforming growth factor beta; Th, T helper; TLR, toll-like receptor; Tregs, T regulatory cells.

Craig S. Lammert and Ethan M. Weinberg contributed equally.

Hispanic ethnicity or Black race are at an increased risk of developing more aggressive forms of AIH.[7,8] Furthermore, there is an increasing trend in the incidence of AIH. In the United Kingdom, the incidence increased from 1.27 to 2.56 per 100,000 people per year from 1997 to 2015,[9] and in New Zealand, the incidence increased from 1.37 to 2.39 per 100,000 people from 2008–2010 to 2014–2016.[10]

AIH exhibits heterogeneity in clinical presentation, ranging from asymptomatic at onset to acute liver failure, and shows diverse laboratory and histological features, which makes diagnosis challenging.[11] The diagnosis and treatment of patients with AIH can be further complicated by overlap and coexistence with other liver disorders.[12,13] Autoimmune liver diseases encompass AIH, primary biliary cholangitis (PBC), and primary sclerosing cholangitis, with each having a distinct profile; however, AIH can also exhibit characteristics of PBC and primary sclerosing cholangitis, which is referred to as "overlap syndrome."[13] While AIH-PBC overlap syndrome affects almost 10% of adults with AIH or PBC, AIH-primary sclerosing cholangitis is primarily reported in children, adolescents, and young adults.[14] It is likely that some cases of cryptogenic cirrhosis represent "burnt-out" AIH.[15] Furthermore, patients with AIH and coincidental metabolic dysfunction–associated steatotic liver disease (MASLD) (AIH-MASLD overlap) require additional attention because corticosteroids, often used in the first-line treatment of AIH, can worsen MASLD.[16]

The differential diagnosis for AIH is broad and heterogeneous, and an accurate integration of all clinical phenomena, laboratory features, and liver histology features is necessary to establish the diagnosis.[11] Serological markers for autoantibodies play a crucial role in the diagnosis of AIH; however, cases of seronegative AIH exist (an average of ~10%), which can lead to underdiagnosis.[11,17] Further, a liver biopsy is necessary for diagnosis and to verify its histological features.[18] The cause of AIH is unknown, but genetics and environmental and immunological factors can influence a patient's susceptibility to developing the disease.[19]

This review aims to provide an overview of the current and emerging therapies used to treat AIH and, most importantly, insight into what patients desire from disease management and treatment strategies.

## Pathophysiology of AIH

The pathogenesis of AIH is complex, involving T cells, macrophages, and plasma cells (PCs) that invade the periportal parenchyma and promote inflammatory immune responses that lead to damage of hepatocytes.[20] Other contributory factors include compromised immunoregulatory mechanisms involving CD8+ cytotoxicity and autoantibody production, and complex interactions between specific genetic traits and molecular mimicry for disease development.[1]

Characteristics of AIH include the presence of autoantibodies, increased IgG, and immune-mediated abnormalities in liver histology.[21] The B-cell activating factor (BAFF), a cytokine that is vital for the survival of transitional and naïve B cells, has been shown to be associated with liver inflammation in AIH.[21,22] Consequently, BAFF is a potential biomarker for diagnosis and a therapeutic target for the treatment of AIH.

In AIH, Ag-presenting cells have an important role in the recruitment and activation of innate immune cells, and they also play a role in activating naïve T cells, consequently triggering responses by the adaptive immune system (Figure 1).[20,23,24] Specifically, hepatic antigenic self-peptides are presented to naïve T cells, leading to the development of T-cell lineages that produce a variety of inflammatory cytokines (eg, IL and interferon-γ).[2,20,25] The presence of IL-12 and IL-4 activate the differentiation of T helper lymphocytes (Th0) into Th1 and Th2 cells, respectively.[20] Th1 cells produce proinflammatory cytokines, activate macrophages through interferon-γ, and stimulate cytotoxic T cells, while Th2 cells produce cytokines to stimulate autoantibody production through B cells that mature into PCs.[20] Consequently, these inflammatory pathways lead to hepatocyte apoptosis and fibrogenesis.[2] Although the pathogenic pathway in AIH has been elucidated, the specific self-Ag that stimulates disease onset or evolution of AIH is yet to be determined.[20]

Studies have indicated that CD4+CD25+ T regulatory cells (Tregs) in patients with AIH are defective in both number and function and, compared with controls, have a significantly lower ability to expand.[26,27] Additionally, at diagnosis, Tregs in patients with AIH are unable to regulate CD8 T-cell proliferation and IL-4 production; however, this ability is restored during drug-induced remission, suggesting a role for immunosuppressive treatment in reconstituting Treg function.[26,28] Moreover, Tregs can also be generated de novo from CD4+CD25− effector cells, offering a potential strategy for generating and expanding Tregs for immunotherapeutic purposes.[26,29]

Another immune system component that has been associated with the pathogenesis of autoimmune liver diseases is the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome.[30] The inflammasome is a multiprotein complex that is expressed in a variety of cells, including macrophages, neutrophils, and microglia, and plays an important role in regulating innate immune responses.[30,31] Activation of the NLRP3 inflammasome is a defense mechanism against pathogen invasion; however, its overactivation can induce inflammation and promote tissue damage and organ dysfunction.[30] Animal models of AIH demonstrate increased

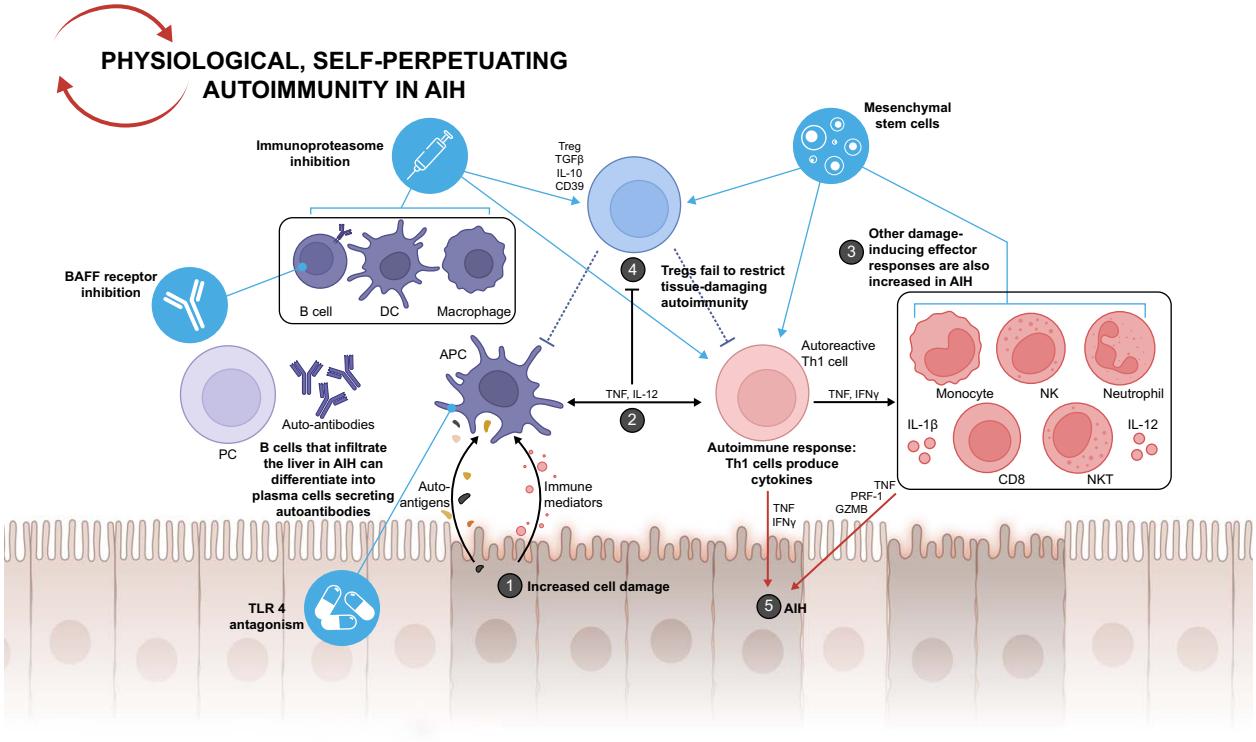


**FIGURE 1** Potential targets for treatment of autoimmune hepatitis. Reprinted from Herkel J, et al. J Hepatol. 2020;73(2):446-448.[23] Copyright © 2020 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved. Abbreviations: APC, Ag-presenting cell; BAFF, B-cell activating factor; CD, cluster of differentiation; DC, dendritic cell; NK, natural killer; NKT, natural killer T-cell; PC, plasma cell; PRF, platelet rich fibrin; TGFβ, transforming growth factor beta; Th, T helper; TLR, toll-like receptor; Treg, regulatory T cell.

expression of NLRP3 inflammasome in the blood[32]; similar observations have been made in mice models of MASLD, with NLRP3 activation driving fibrosis and progression to metabolic-associated steatohepatitis.[33] Further, the NLRP3 inflammasome has been implicated in MASLD progression, with studies reporting a higher level of NLRP3 components in patients with metabolic-associated steatohepatitis compared with those without metabolic-associated steatohepatitis.[34]

## Current treatment approaches for AIH

The treatment objectives for AIH are symptom resolution, halting liver inflammation and progression of hepatic fibrosis, and achieving and maintaining disease remission. Although biopsy is the gold standard for disease surveillance, complete biochemical remission and improvements in liver stiffness based on transient elastography are reliable surrogates for histological disease activity and fibrosis regression and may be considered a less invasive option.[11,35] Complete biochemical remission is defined as the normalization of serum transaminases and IgG within 6 months of treatment initiation.[36] Although noninvasive fibrosis measures are increasingly available, they still lack validation in AIH. Failure to achieve complete biochemical remission is defined as an "insufficient response," which is a potential predictor of a poor prognosis in AIH.[36]

The standard treatment for AIH includes steroid induction therapy followed by maintenance therapy with nonsteroidal immunosuppressants.[18,37] For first-line therapy, the American Association for the Study of Liver Diseases (2019 Guidelines) recommends prednisolone or budesonide, with or without immunosuppressive azathioprine, a steroid-sparing agent.[2] All patients with AIH are candidates for therapy—except individuals with inactive disease by clinical, laboratory, and histological assessment.[2]

For maintenance therapy, several second-line and third-line treatment options exist. These include tacrolimus, mycophenolate mofetil (MMF), and biologics.[2,38] Patients with AIH can be treated with MMF as both first-line treatment option and second-line in patients who are unable to tolerate azathioprine.[2,39] Compared with azathioprine, MMF has been associated with better outcomes in patients with treatment-naïve AIH,[40,41] and a meta-analysis reported a pooled response rate of 58% for MMF.[42] However, MMF is associated with teratogenic effects and should be discontinued or avoided in patients who are considering pregnancy.[18] In patients with AIH who are refractory to standard therapy, a recent meta-analysis indicated that tacrolimus is a potential treatment option that is safe and effective.[43] Further,

potential salvage treatments for treatment-refractory AIH include cyclosporine, rituximab, and infliximab, an anti-TNF-α monoclonal antibody.[2,38,44] It should be noted that, although the event is rare, TNF-α inhibitors can potentially induce de novo AIH.[45,46] Drug-induced AIH can present with characteristics of AIH, including positive autoantibodies and interface hepatitis on liver biopsy.[47] Overall, there is a lack of consensus on the management of patients with AIH, especially in the second-line and third-line treatment of those with difficult-to-treat disease.[48] This is likely driven by a reliance on case reports, rather than clinical trial data, for second-line and third-line treatment, which makes it difficult to extrapolate across patient populations.[49]

Despite AIH being recognized for a longer period than hepatitis C, therapeutic progress for AIH has been minimal. The latest development for AIH treatment was the incorporation of budesonide into the treatment paradigm, based on the findings of Mann et al, 2010.[18,50] Despite being a corticosteroid immunosuppressive agent, budesonide is associated with fewer steroid-specific side effects than other corticosteroids, which is attributed to its 90% first-pass effect in the liver.[50,51] Its use in AIH has been investigated by several studies, including 1 multicenter, randomized, double-blind trial comparing budesonide with prednisone as first-line therapy.[50] In this study, Mann et al found that budesonide combined with azathioprine improved induction and maintenance of remission and had a lower incidence of steroid-specific side effects than prednisone combined with azathioprine.[50] Budesonide was later recommended as treatment for patients with AIH without cirrhosis because portal hypertension, a complication of cirrhosis, may lead to systemic exposure due to decreased first-pass effect in the liver.[2,18,52] However, evidence regarding the effectiveness of budesonide in AIH is conflicting. Real-life data from a Spanish registry indicated that budesonide is inferior to prednisone as first-line treatment in patients with AIH, with a significantly lower biochemical response rate.[53] In addition, the effect of budesonide with azathioprine on biochemical remission did not differ significantly compared with prednisone plus azathioprine in pediatric patients with AIH.[54]

Currently, available treatments for AIH are not specific or targeted, and consequently, they have broad immunosuppressive effects and are associated with serious side effects.[24] Predniso(lo)ne, when taken long term, increases the risk for bone fractures, cataracts, and diabetes.[55] A study reported corticosteroid-specific adverse events in 120 of 476 patients (25%) on long-term maintenance treatment for AIH.[55] Azathioprine is widely used as a long-term treatment in conjunction with corticosteroids; however, it can induce cholestatic hepatitis.[2,56] In addition to DILI, side effects of azathioprine include pancreatitis, nausea and vomiting, rash, bone marrow suppression, veno-occlusive disease, opportunistic infections, and malignancy.[51]

While steroids remain an essential part of induction therapy in AIH, the identification of a steroid-free disease maintenance regimen is important.

## POTENTIAL FOR TARGETED TREATMENT OF AIH

Historically, autoimmune diseases have been treated primarily with corticosteroids to suppress the aberrant immune response.[57] In recent years, there has been a shift away from inducing broad immunosuppression to immunomodulation for several autoimmune diseases by targeting specific inflammatory mediators implicated in the disease.[57] Several targeted immunomodulatory treatments have gained approval for various autoimmune diseases, including plaque psoriasis, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus.[38] Existing immunomodulatory treatments for these autoimmune diseases may provide a rationale for use in patients with AIH,[38] and they may already be used in patients with indicated autoimmune comorbidities. Among these treatments, rituximab, a monoclonal antibody that depletes B cells by targeting CD20, has been associated with improvements in patients with difficult-to-manage AIH. In a study of 22 patients with AIH, rituximab improved liver function and reduced clinical disease flares and the use of corticosteroids.[58]

In addition to B cells, there are several other potential targets for AIH based on its proposed pathophysiology involving T cells, PCs, and monocytes producing increased levels of TNF-α.[59] A breakthrough in the mechanistic understanding of AIH would potentially foster emergence of additional novel therapeutic targets that would lead to improved patient outcomes, as seen with other autoimmune diseases. In addition to the potential of existing targeted therapies from other autoimmune diseases in AIH, ongoing clinical investigations are exploring other targets of interest.

## THERAPIES IN DEVELOPMENT FOR AIH

There are several emerging therapies for AIH, each with a distinct mechanism of action (Table 1).

Zetomipzomib (KZR-616; Kezar Life Sciences, San Francisco, CA) is a first-in-class, small-molecule, selective immunoproteasome inhibitor that is currently being investigated in a randomized, double-blind, placebo-controlled, phase 2a clinical trial in patients with AIH who have not benefited from the standard of care or have relapsed (PORTOLA; NCT05569759).[64,65]

Immunoproteasomes are predominately expressed in immune cells, in which they modulate multiple

**TABLE 1** Ongoing clinical trials in autoimmune hepatitis

| Trial name | Trial identifier | Phase | Start/end date | Proposed mechanism of action |
|---|---|---|---|---|
| A study of zetomipzomib (KZR-616) in patients with AIH (PORTOLA) | NCT05569759 | Phase 2 | May 2023/ March 2025 | Selective inhibition of the immunoproteasome, leading to broad immune modulation[60,61] |
| ADCC-mediated B-cell depletion and BAFF-R blockade (AMBER) | NCT03217422 | Phase 2/3 | February 2018/ December 2025 | ADCC-mediated B-cell depletion through BAFF inhibition[38] |
| Liver test study of using JKB-122 in AIH patients who are refractory or intolerant to current therapies | NCT02556372 | Phase 2 | April 2016/ January 2019 | TLR4 inhibition leading to the reduction of proinflammatory cytokines[37,62] |
| Selected mesenchymal stromal cells to reduce inflammation in patients with PSC and AIH (Merlin) | NCT02997878 | Phase 1/2 | December 2018/ December 2023 | Induction of Treg differentiation and suppression of lymphocyte activation[63] |

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AIH, autoimmune hepatitis; BAFF, B-cell activating factor; BAFF-R, B-cell activating factor receptor; PSC, primary sclerosing cholangitis; TLR, toll-like receptor; Treg, regulatory T cell.

immune effector cell functions, including the processing of intracellular Ag for presentation by the major histocompatibility complex class I.[60] Expression of the immunoproteasome is also induced in nonimmune cells in the setting of inflammation, and the increased activity of immunoproteasomes has been observed in several autoimmune diseases, including in liver cells of patients with chronic active hepatitis or cirrhosis.[60,66] Immunoproteasomes impact inflammatory disease processes through their effects on T cells, macrophages, and B cells.[60] Selectively targeting the immunoproteasome results in broad immunomodulatory activity across both the innate and adaptive immune systems, resulting in decreased production of proinflammatory cytokines (eg, TNF-α, IL-23, IL-6, and IL-17), decreased activity of inflammatory T helper 1 and 17 cell subsets, increased number of regulatory T cells, and decreased PC and autoantibody production, without leading to immunosuppression.[60,61,67–69]

Ianalumab (VAY736; MorphoSys, Boston, MA) is a monoclonal antibody that is being studied in a randomized, placebo-controlled, double-blind, dose-ranging phase 2/3 clinical trial in patients with AIH with incomplete response or who are intolerant of standard-of-care treatment (AMBER; NCT03217422).[70] Ianalumab targets the BAFF receptor of the tumor necrosis family, leading to antibody-dependent cellular cytotoxicity–mediated B-cell depletion, and competitively inhibits binding of the BAFF ligand to its receptor.[38] It has been shown that BAFF plays a vital role in B-cell development and proliferation.[20] Furthermore, overexpression of BAFF has been reported in several autoimmune diseases.[71] Studies have shown that in patients with AIH, BAFF levels were higher than in healthy controls, and high levels of BAFF and normal levels of IL-21 were associated with higher bilirubin, suggesting more liver dysfunction.[72,73]

JKB-122 (Biostax Corp., Orlando, FL) is a small-molecule, long-acting toll-like receptor 4 antagonist that was evaluated in a phase 2 clinical trial in patients with AIH who were refractory to or intolerant of current therapies (NCT02556372).[74,75] Toll-like receptors can recognize pathogen-derived molecules unique to bacteria and viruses, leading to signaling and activation of the innate and adaptive inflammatory responses.[76] In the setting of AIH, toll-like receptor 2/4 ligands can induce the release of large quantities of proinflammatory cytokines that cause rapid apoptosis and necrosis of hepatocytes.[59,62] In an AIH mouse model, JKB-122 caused inhibition of proinflammatory cytokines in serum and liver and showed dose-dependent biochemical and histological improvement.[37]

Cell therapy with mesenchymal stem cells (MSCs) is an approach that has been investigated in autoimmune liver diseases because of their potential for differentiation, antifibrosis properties, and immunomodulatory effects, including the ability to suppress lymphocytes

and promote Tregs.[63] MSCs can interact with macrophages, natural killer cells, dendritic cells, neutrophils, and mast cells to induce tolerogenic activity in the immune system, which consequently has a beneficial effect on autoimmune disorders.[63] In a mouse model for experimental AIH, the use of bone marrow MSCs reduced experimental AIH in a dose-dependent manner.[63,77] However, the use of MSC should be carefully monitored due to its ability to also enhance tumor growth.[63]

The Merlin study (NCT02997878) is an adaptive, single-arm, multicenter, phase 2a multi-disease clinical trial to determine the dose safety of ORBCEL-C™ (Orbsen Therapeutics, Galway, Ireland), highly purified stromal cells isolated from the human umbilical cord, and evaluate its treatment activity through assessment of biomarkers.[78]

## Challenges of conducting clinical trials in AIH

There are several challenges in conducting and interpreting the results of clinical trials for AIH. As AIH is a rare disorder, recruitment for AIH clinical trials requires a multicenter approach to enroll an adequate number of patients.[79] It is essential to design clinical trials that focus on patients who responded insufficiently to standard treatment or first-line treatment, as these patients are at greatest risk for disease progression.[80] Lastly, it is well recognized that clinical trials have not historically included patients from diverse racial and ethnic backgrounds.[81] This is particularly problematic given that Asian, Black, Hispanic, and male patients with AIH have poor prognosis, and it is therefore critical that they are represented in clinical trials to create equality and a holistic view of the disease.[7,8]

The design of clinical trials should consider the manifestation type of AIH (first presentation of AIH or severe AIH), treatment type (first-line/second-line therapies or maintenance treatment), and primary outcome (short-term vs. long-term clinical benefits for patients with AIH).[79] Effective trial design and endpoints should be re-evaluated, especially for first-line and second-line treatment studies.[80] Complete biochemical remission after 6 months has been proposed as a primary end point for first-line treatments, while histological disease activity at 12 months has been proposed as a primary end point for second-line treatment.[36,80] Endpoints related to dependence on steroids (eg, dose, rate of withdrawal, and steroid-related side effects) have been proposed as secondary end points for both first-line and second-line treatments.[80] Overall, the heterogeneity of AIH can also make it difficult to extrapolate the results of clinical trials to a broader population of patients with AIH.[82] Future interventional studies should focus on key unmet needs for 3 patient groups: (1) induction therapy for treatment-naïve patients, (2) second-line treatment for patients who are intolerant of standard therapy, and (3) treatment alternatives for patients with poor treatment response.[83] Addressing these challenges is crucial for advancing the understanding and management of AIH.

# PATIENT PERSPECTIVE

Understanding patients' health-related quality of life enhances the management of AIH, specifically as it relates to patient, disease, and physician factors.[84] Medication side effects and intolerance are also critically important to AIH patients. In January 2023, the Autoimmune Hepatitis Association (AIHA) hosted an externally led patient-focused drug development meeting (E-LPFDD) on AIH (available at https://www.youtube.com/watch?v=DbyteMM3qo8) with the aim to share first-hand patient accounts of AIH and management. A majority of attendees (56%) reported "treatment should have less side effects" as the most important change needed for treatments. Other important aspects of treatment included improvement of disease symptoms (17%), not requiring daily oral therapy (10%), and effective at normalizing liver tests (10%).[85] Given the adverse effects caused by long-term immunosuppression treatment, it is essential that patients are monitored to ensure a favorable risk-benefit balance.[20] Furthermore, there may be a preference among patients for long-acting injectable treatment over daily oral medications.[86,87] For diagnosis, the use of liver biopsies is valuable; however, liver biopsies are also associated with significant risks, including bleeding complications.[88] Overall, patients desire better, noninvasive diagnostics and tests for disease monitoring, compared with current biomarkers that require biopsies. Specifically, a biomarker that is both sensitive and specific would be highly desirable. This has implications in clinical trials as well as 31% of E-LPFDD participants reported that the "requirement of liver biopsy" would be the biggest barrier to participation in a new drug study for AIH.[85]

## Unmet needs in treatment

Improvements in treatment strategies for AIH should focus on a steroid-sparing approach to minimize steroid-induced side effects, especially for long-term disease management. There is a need for individualized treatment approaches for patients with AIH. A better understanding of the underlying mechanisms of AIH will lead to a treat-to-target approach similar to that for other autoimmune diseases. Specifically, for patients with B-cell–driven disease (elevated IgG and PCs), anti-CD20 therapy may be most effective, while a T-cell–

targeted therapy may be more appropriate for patients with T-cell–driven disease. In patients in whom the predominant disease mechanism is unclear, a broader approach targeting several disease mediators may be the most effective option.

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