Evolution of Therapy in Autoimmune Hepatitis

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Abstract: Autoimmune hepatitis (AIH) is an immune-mediated liver disease characterized by a spectrum of clinical manifestations, ranging from asymptomatic liver enzyme abnormalities to fulminant liver failure. Despite significant achievements, the backbone of first-line AIH treatment, including corticosteroids and azathioprine, has remained nearly unchanged for 5 decades. However, up to 20% of patients experience insufficient response, loss of response, or treatment intolerance. For patients intolerant to first-line therapy, second-line options include mercaptopurine and mycophenolate mofetil (MMF), with recent debates regarding MMF's potential role in first-line treatment. A significant advancement has been the tailoring of azathioprine doses and manipulating blood levels with the addition of low-dose allopurinol by using therapeutic metabolite monitoring for patients with insufficient or lost biochemical response. Increasing experience with calcineurin inhibitors and biologic agents, particularly rituximab and infliximab, has demonstrated their efficacy as third-line options. Notably, B-cell activating factor blockade emerges as a promising future treatment. This article delves into the chronological evolution of AIH treatment, focusing on recent advances.

Keywords
Autoimmune hepatitis, treatment, biochemical remission, immunosuppression, management

Autoimmune hepatitis (AIH) is an immune-mediated liver disease with characteristic histologic findings and favorable response to immunosuppression. AIH can impact individuals of all ages and ethnicities and has a female predominance.[1] The etiology of AIH is multifactorial, involving genetic predisposition, environmental triggers, and a dysregulated immune response.[2] If not recognized and promptly treated, AIH can lead to cirrhosis, liver failure, liver transplantation, and death. The incidence and prevalence of this disease are rising worldwide with an incidence of 1.28 cases per 100,000 person-years and pooled prevalence over the past 10 years of approximately 27.91 per 100,000.[3] The rising burden of disease makes early recognition and treatment essential. The goal of treatment is to decrease liver-related complications and improve quality of life. Despite advances in the understanding of AIH pathogenesis

Table. International Autoimmune Hepatitis Group Definitions of Therapy Response

Therapy response	Definition	Time frame
Complete biochemical response	Serum transaminase normalization and IgG below the ULN	Within 6 months of treatment initiation
Insufficient response	Lack of complete biochemical response	No later than 6 months after treatment initiation
Nonresponse	<50% reduction of serum transaminase	After 4 weeks of treatment
Remission	HAI of 0-3/18	After 12 months of treatment or where clinically indicated
Intolerance	Any adverse event related to treatment as assessed by treating physician and leading to discontinuation of the drug	Any time after treatment initiation

HAI, histology activity index; IgG, immunoglobulin G; ULN, upper limit of normal.

and clinical presentations, challenges remain in managing refractory cases and minimizing long-term side effects of therapy. This article aims to provide an overview of AIH, including its definition, types of presentation, response to therapy, and evolving therapies, with an emphasis on recent advancements and future directions.

Diagnostic Criteria

AIH is diagnosed based on a synthesis of clinical presentation, biochemistry, serology, and histologic findings. The International Autoimmune Hepatitis Group (IAIHG) initially proposed diagnostic criteria in 1993 comprised of histologic parameters, autoantibodies, presence of genetic factors (human leukocyte antigen D8-DR3 haplotype or DR4 allotype), and response to therapy. The 1999 revised criteria removed response to therapy, as there are too many confounding factors with respect to therapy response.[4] However, response to therapy remains an important clinical parameter. In 2008, the IAIHG developed simplified criteria for use in clinical practice with specificity of 97% for probable and 99% for definitive AIH.[5] This scoring system is used for chronic AIH based on the presence of antibody positivity, immunoglobulin G (IgG) levels, liver histology, and exclusion of viral hepatitis. The original and revised IAIHG criteria were intended primarily for research purposes. In the setting of acute onset AIH, the revised criteria perform better than the simplified criteria.[6]

Ruling out alternative etiologies is essential in the diagnosis of AIH, as many liver diseases can resemble AIH, including Wilson disease, viral hepatitis, and drug-induced liver injury. Drug-induced autoimmune-like hepatitis (DI-ALH) can have biochemical, serologic, and histologic features that may be indistinguishable from AIH. Although not the focus of this article, identifying DI-ALH is crucial because the culprit medication must be stopped and these individuals seldom require long-term immunosuppression.[7] Furthermore, AIH can coexist with other immune-mediated liver diseases in variant forms.

Clinical Presentations

Clinically, AIH has a wide spectrum of presentations from asymptomatic liver enzyme abnormalities incidentally noted on routine testing to fulminant liver failure.[8] In a Canadian study, 31 of 125 patients with AIH were asymptomatic at presentation, and referral was prompted by abnormal liver test results.[8] Asymptomatic individuals were noted to have either burned-out cirrhosis or mildly active chronic hepatitis at the time of diagnosis.[8] Up to one-third of patients with AIH have cirrhosis at the time of diagnosis.[8] In asymptomatic individuals, treatment prevents or delays fibrosis progression and improves survival.[9]

Symptoms can be nonspecific and include fatigue, malaise, abdominal pain, and arthralgias. Biochemical response, with normalization of liver enzymes and IgG at 6 months, occurs in 60% to 80% of patients started on treatment.[10,11] More severe presentations may include jaundice, with the most severe being acute or acute-on-chronic liver failure, which requires prompt treatment initiation and recognition of lack of response leading to the need for transplantation.[12]

Acute presentations fall into 2 distinct categories: acute exacerbations of chronic disease or acute AIH without chronic histologic changes. Early recognition of nonresponse to corticosteroids and timely liver transplantation can be lifesaving.[13] Acute-icteric AIH represents patients with jaundice without coagulopathy (international normalized ratio [INR] <1.5) or encephalopathy. These individuals have overall favorable corticosteroid response of more than 80%.[14] Acute severe AIH (AS-AIH) presents with jaundice and coagulopathy (INR >1.5)

without encephalopathy. In AS-AIH, delayed initiation of corticosteroids after 5 days of presentation is associated with clinical nonresponse and need for liver transplantation.[15] INR at corticosteroid initiation and lack of improvement of INR and bilirubin at day 3 can be used to predict nonresponse to corticosteroids and need for liver transplantation in patients with AS-AIH.[16] AS-AIH with encephalopathy characterizes AIH with acute liver failure (ALF-AIH).[13] Corticosteroid therapy is effective in up to 40% of individuals with ALF-AIH, and ALF-AIH patients should be assessed for liver transplantation.[17]

Definition of Response to Therapy

The primary goals of AIH treatment are to achieve and maintain remission to prevent progression to cirrhosis, liver failure, and death while sustaining patient quality of life. Response to therapy definitions have evolved since first described by the IAIHG in 1993 when response was categorized as complete, partial, no, treatment failure, or relapse.[18] Many studies use biochemical remission as an endpoint in reference to individuals with normalization of hepatocellular enzymes and IgG. Based on updated IAIHG consensus in 2022,[19] treatment endpoints are summarized in the Table. Complete biochemical response describes normalization of serum transaminases and IgG below the upper limit of normal. Complete biochemical response should be achieved within 6 months of treatment initiation. Insufficient response reflects lack of complete biochemical response without normalization of transaminases and IgG no later than 6 months after treatment initiation. This definition applies to both first- and second-line therapy and only after adherence to medical therapy has been confirmed. In the case of azathioprine, 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) levels can be used when available to monitor, with low levels of both indicating either insufficient dosing or nonadherence and high levels of 6-TG increasing risk of adverse drug reactions.[20] Nonresponse is defined as less than 50% reduction of serum transaminases, with serum transaminases remaining above the upper limit of normal, after 4 weeks of treatment. Remission is not determined biochemically and is instead histologic. The histology activity index (HAI) provides graded scores in each of the following categories: periportal with or without bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis.[21] Remission is defined as an HAI of 0 to 3 out of 18. Biopsy for the purpose of remission assessment can be performed 12 months after treatment initiation or at any other time point during treatment if clinically indicated. Intolerance to treatment describes any adverse event possibly related to potential discontinuation of the drug. This takes into account corticosteroid-related side effects, including hypertension, diabetes, osteoporotic fractures, psychosis, and acne, as well as side effects related to immunomodulator therapy, including cytopenia, gastrointestinal symptoms, hepatitis, pancreatitis, and allergic reactions.

It is estimated that 10% to 15% of individuals with AIH are refractory to standard treatment defined as failure to achieve response despite adequately dosed standard immunosuppressive therapy.[2] This may be the result of incomplete compliance with medication or true nonresponse.[22] Additionally, in the case of variant syndromes, liver biochemistry may not normalize owing to ongoing activity of the coexisting liver disease.[22] Refractory disease poses significant clinical challenges and necessitates alternative therapeutic strategies. Careful review to ensure the correct diagnosis and adherence to treatment is vital prior to applying the label of refractory disease.

First-Line Treatment

For more than 50 years, the mainstay of first-line treatment for AIH has relied on corticosteroids to induce remission, followed by thiopurine therapies for maintenance of remission.[23]

Corticosteroids

The initial corticosteroid trials for AIH conducted in the early 1970s are among the earliest randomized trials in modern medicine and demonstrated the significant survival benefit of prednis(ol)one therapy in patients with AIH. Five-year survival rose significantly from 25% without treatment to 80% with long-term corticosteroid therapy.[24] Although the optimal dosage of corticosteroids for remission induction remains a topic of debate, a European multicenter study found no significant difference in achieving biochemical remission between high-dose and low-dose regimens, suggesting that both approaches may be effective. This study compared prednisolone greater than 0.5 mg/kg/day (median starting dose 50 mg/day) with less than 0.5 mg/kg/day (median starting dose 20 mg/day). Biochemical remission rates were 70.5% vs 64.7%, respectively (P=.20).[25] This finding is reflected in the European Association for the Study of the Liver (EASL) clinical practice guideline, which acknowledges the lack of a definitive optimal dose by proposing a broad prednisolone dose range of 0.5 to 1 mg/kg/day, allowing for some degree of variation in clinical practice.[22] For the majority of cases, 0.5 mg/kg/day of prednisolone effectively induces remission.

Decades after establishing corticosteroids as the mainstay of treatment, a landmark study in 2010 supported budesonide, a liver-targeted corticosteroid, as a potential alternative for patients without cirrhosis. This

large-scale randomized controlled trial (RCT) showed budesonide combined with azathioprine to be effective in inducing and maintaining remission with fewer corticosteroid-related side effects.[26] This is particularly appealing because of budesonide's high first-pass hepatic clearance (>90%) and favorable side-effect profile. However, the presence of cirrhosis or advanced fibrosis may limit treatment success and increase the risk of adverse events owing to high first-pass hepatic clearance.[27] In this study, the fixed prednisone weaning regimen may explain the comparable biochemical response rate with budesonide. A recent retrospective multicenter study from Spain suggests that budesonide might be less effective as a first-line therapy. Although chosen for cases with less disease activity, budesonide achieved significantly lower complete biochemical response rates (49%, n=105) compared with prednisolone (87%, n=276).[28]

Azathioprine

Shortly after the introduction of corticosteroids, azathioprine trials were performed in the early 1970s. Initial studies showed that both prednisone monotherapy and combination therapy with low-dose azathioprine (50 mg/day) achieved clinical, biochemical, and histologic improvement, as well as survival benefit. In contrast, azathioprine monotherapy was similar to placebo.[29] Subsequent head-to-head RCTs also further revealed that prednisone monotherapy was superior to azathioprine monotherapy in terms of normalizing IgG and improving overall survival.[30] Another RCT demonstrated that prednisone with azathioprine achieved significantly more frequent histologic remission and caused less severe and less frequent side effects than prednisone alone over a 3-year follow-up.[31]

Two decades following initial reports of unsuccessful treatment with azathioprine alone, a controlled trial conducted at King's College Hospital yielded a significant breakthrough. In this study, 72 individuals with histologically confirmed AIH received 1 year of both prednisolone and azathioprine. At 1 year, the prednisolone was withdrawn and higher doses of azathioprine continued. A total of 83% of patients remained in remission with median follow-up of 67 months.[32] This finding helped establish the combination of low-dose corticosteroids and azathioprine as the standard-of-care treatment for the following decades. Current treatment approaches reflect this established practice, but with some key differences. The EASL clinical practice guideline recommends initiating corticosteroid therapy with a flexible dose range of 0.5 to 1 mg/kg/day, followed by the addition of azathioprine 2 weeks later. Azathioprine is typically started at a low dose of 50 mg/day and gradually increased up to a maximum of 1 to 1.5 mg/kg/day.[22] In contrast, the American Association for the Study of Liver Diseases (AASLD) guideline suggests a fixed-dose approach using either a combination of 30 mg/day prednisolone with 50 mg/day azathioprine or prednisolone monotherapy at 60 mg/day. The AASLD guideline favors corticosteroid monotherapy for specific patient groups, such as those with cytopenia, malignancy, thiopurine methyltransferase deficiency, or pregnancy. Conversely, combination therapy is preferred for patients with increased risk of adverse events with corticosteroids such as postmenopausal status, osteoporosis, uncontrolled metabolic conditions, or emotional instability.[33]

Azathioprine metabolite monitoring in AIH with tailoring of the azathioprine dose was a milestone of the early 2000s and supports a personalized medicine strategy.[34] In a subsequent retrospective analysis, our group demonstrated that monitoring 6-TG metabolite levels led to significantly higher occurrence of biochemical remission at 6 months (77% vs 60%; P=.008) and significantly fewer adverse drug reactions (44% vs 86%; P=.0002) compared with a weight-based azathioprine dosing regimen.[20] A recent multicenter retrospective study across 4 European centers further solidified the value of metabolite monitoring. The study evaluated 337 patients with AIH of whom 146 underwent monitoring of both 6-TG and 6-MMP levels at multiple time points over 4 years. This study suggests an optimal 6-TG level cutoff of at least 223 pmol/0.2 mL for maintaining long-term biochemical remission. Importantly, the study found that simply increasing the azathioprine dose did not guarantee optimal 6-TG levels, but could instead elevate 6-MMP levels, increasing the risk of side effects. Administration of low-dose thiopurine with allopurinol was found to be effective in modifying metabolite profiles and achieving sustained remission even in patients with a poor response to standard therapy.[35]

The latest clinical practice guidelines from EASL and AASLD show consensus on the standard first-line treatment for AIH. However, debate continues regarding the treatment of patients who experience inadequate biochemical remission or who are intolerant to these therapies.[22,33]

Second-Line Treatment

Approximately 20% of patients experience insufficient response or intolerance to first-line therapy, necessitating exploration of alternative treatment approaches.[36,37] The European Reference Network on Hepatological Diseases (ERN RARE-LIVER) and the IAIHG recommend mercaptopurine or mycophenolate mofetil (MMF) as second-line therapy for AIH patients who are intolerant to azathioprine. For patients with insufficient response to standard therapy, the ERN RARE-LIVER statement advocates for intensification through measurement of 6-TG.

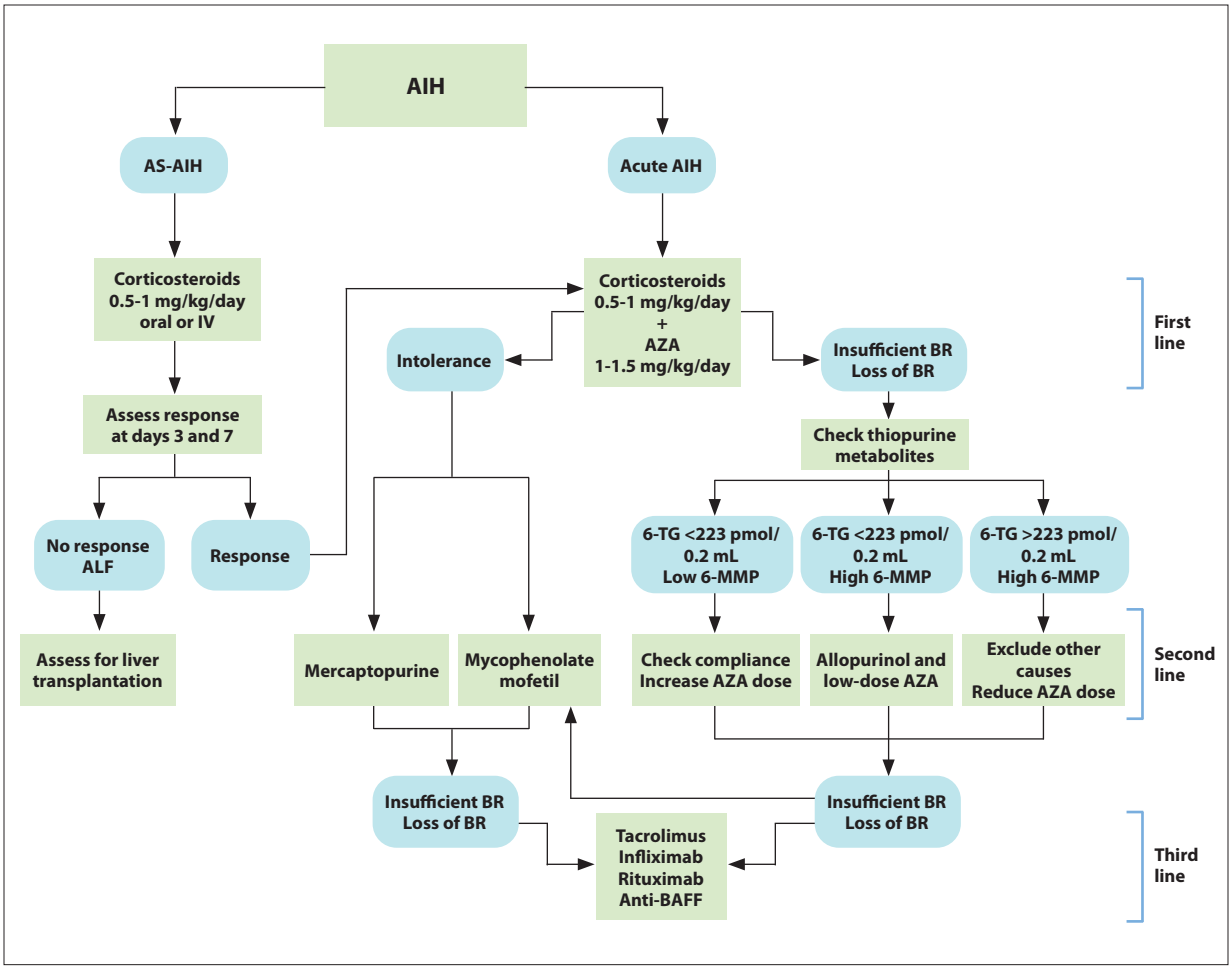

Figure 1. Algorithm for the management of AIH based on current guidelines and latest evidence. The current treatment strategy is based on induction with corticosteroids and AZA as the standard-of-care approach. For patients who are intolerant to AZA, second-line alternatives include either mercaptopurine or mycophenolate mofetil. For patients with insufficient response or loss of response during follow-up with AZA, the recommended approach is to check metabolites. For patients with low 6-TG and low 6-MMP levels, the next step is checking compliance and increasing AZA. For patients with low 6-TG but high 6-MMP levels, the next step is to add allopurinol and reduce AZA. For patients with high 6-TG and high 6-MMP levels, AZA doses should be reduced, and alternative or coexisting diagnoses should be ruled out. In patients with insufficient biochemical response or loss of biochemical response to second-line treatments, tailoring one of the third-line treatments according to the patient's clinical condition is advised.

6-MMP, 6-methylmercaptopurine; 6-TG, 6-thioguanine; AIH, autoimmune hepatitis; ALF, acute liver failure; AS-AIH, acute severe AIH; AZA, azathioprine; BAFF, B-cell activating factor belonging to the tumor necrosis factor family; BR, biochemical remission; IV, intravenous.

This 6-TG–based approach involves a tiered strategy. Patients with high 6-TG levels (above 220 pmol/0.2 mL) should be re-evaluated to rule out alternative or coexisting diagnoses followed by trialing alternative therapies such as MMF or any of the third-line treatments. In patients with low 6-TG levels (below 220 pmol/0.2 mL), medication adherence must be addressed. If the medication is being taken as prescribed, the next step is to increase the dose or add allopurinol to shunt the metabolic pathway away from hepatotoxic 6-MMP and toward 6-TG.[23] Recent European multicenter data suggest measuring both 6-TG and 6-MMP levels together, which might further refine this approach. For patients with low 6-TG and low 6-MMP, adherence to azathioprine should be confirmed and dose escalation considered. Conversely, patients with low 6-TG but high 6-MMP levels may benefit from the addition of allopurinol alongside azathioprine dose reduction. In cases of high 6-TG and 6-MMP, azathioprine dose reduction and investigation for alternative or coexisting diagnoses are recommended (Figure 1).[35]

Mercaptopurine

There is currently no high-quality evidence definitively demonstrating the effectiveness of mercaptopurine for AIH patients who do not respond to azathioprine. The rationale for using mercaptopurine in azathioprine-intolerant AIH patients primarily stems from small case series and the assumption of similar efficacy to azathioprine. A retrospective study of 22 AIH patients switched to mercaptopurine after azathioprine intolerance found a 75% success rate in achieving partial or complete biochemical response. However, the remaining patients also experienced intolerance to mercaptopurine.[38] Studies from the inflammatory bowel disease literature demonstrate tolerability to mercaptopurine when azathioprine needed to be stopped because of nausea, vomiting, flu-like illness, or rash.[39]

Mycophenolate Mofetil

MMF is the most extensively studied alternative maintenance therapy to azathioprine. Since 2000, case series have reported promising outcomes for MMF use in AIH patients intolerant to azathioprine.[38,40,41] A multicenter retrospective cohort study in 2017 examined the efficacy of MMF (0.5-2.0 g/day) as a second-line therapy. The study included 121 patients: 74 who were intolerant to azathioprine and 47 who were nonresponders to first-line therapy. The study found that 57% of azathioprine-intolerant patients and 34% of nonresponders achieved complete biochemical remission. Importantly, 91.9% of patients across both groups maintained biochemical response.[42] A meta-analysis evaluating second-line MMF therapy, involving 397 patients across 12 studies, demonstrated an 82% biochemical response rate in the azathioprine-intolerant group and a 32% response rate in azathioprine nonresponders. Notably, the discontinuation rate for MMF therapy remained low at 8%.[43] Initial investigations into MMF as a first-line treatment for AIH emerged in 2011 and 2016, stemming from a single-center study conducted in Greece.[44,45] The complete response rates with MMF-prednisolone combination therapy were 59.3% (35/59 patients) and 71.6% (78/109 patients), respectively, in these studies. Additionally, the ability to maintain remission off prednisolone was 37% (22/59 patients) and 78.2% (61/78 patients) in the respective studies. A more recent propensity score–matched study by the same group directly compared MMF with azathioprine as first-line therapy, with 32 patients in each group.[46] Both groups received prednisolone (0.5-1 mg/kg/day) alongside either azathioprine (1-2 mg/kg/day) or MMF (1.5-2 g/day). Although complete biochemical response rates at 6 and 12 months were similar between the groups, MMF treatment was associated with a significantly higher rate of corticosteroid-free biochemical remission at the end of follow-up (median >3 years). Septicemia was the only major adverse event reported, affecting 3 patients across all studies.[44-46] Notably, in the propensity score–matched comparison, the azathioprine group experienced a 28.1% rate of intolerance, whereas none of the patients in the MMF group discontinued treatment owing to severe side effects. However, 3 patients in the MMF group experienced temporary discontinuation for 1 to 2 weeks owing to infection.[46]

The Dutch AIH Study Group addressed a critical gap in knowledge by conducting the first and only RCT directly comparing azathioprine and MMF for treatment-naive AIH patients. The primary endpoint of the CAMARO trial was the normalization of serum alanine aminotransferase (ALT) and IgG levels after 24 weeks of treatment. The MMF group achieved a significantly higher rate of this primary endpoint compared with the azathioprine group (56.4% vs 29.0%; P=.022). Notably, no serious adverse events were reported in the MMF group, whereas 4 patients in the azathioprine group experienced such events (12.9%; P=.034).[47] This trial undoubtedly represents a significant advancement in the evolution of treatment options for AIH. However, given that it is the sole RCT to date, the findings should be cautiously interpreted for clinical practice. Furthermore, MMF is a known teratogen and should be avoided in individuals with childbearing potential. The study period was only 6 months, and there were no data on long-term transplant-free survival, histologic remission, or sustained remission after withdrawal of corticosteroids. Moreover, nearly half of the participants had a compatible rather than typical histology and one-third had probable diagnosis of AIH based on the simplified IAIHG criteria. Response rates reported with combined azathioprine and corticosteroid induction of 29% were far below those reported in previous studies.[32]

Safety profiles of MMF and azathioprine appear comparable in terms of leukopenia and serious infections. However, azathioprine carries a significantly higher risk of gastrointestinal side effects, including nausea, diarrhea, pancreatitis, and hepatotoxicity. This translates to a higher rate of treatment discontinuation owing to adverse events compared with MMF therapy.[43,46-48] Furthermore, a meta-analysis of 32 studies on solid organ transplantation suggests a lower risk of developing cancer with MMF compared with azathioprine. This includes skin cancer, lymphoproliferative disorders, and solid organ malignancies.[49]

Third-Line Treatment

Calcineurin Inhibitors

Several alternative treatments have been explored for complete or partial treatment failure with conventional therapies; however, many are only supported by evidence from small case series. Calcineurin inhibitors (CNIs),

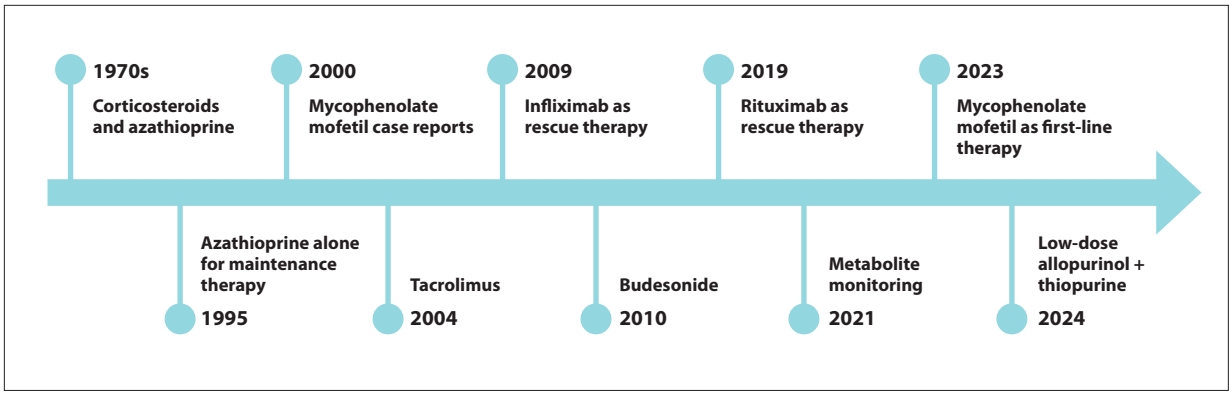

Figure 2. Timeline of autoimmune hepatitis treatments.

particularly tacrolimus, are the most frequently used third-line option in clinical practice for AIH. Cyclosporine has been tried in AIH since the early 1980s, nearly 2 decades before tacrolimus, but the experience with tacrolimus is much more extensive. The relatively widespread use of tacrolimus has led some authors to advocate for considering it as a second-line treatment alongside MMF.[50] An initial Mayo Clinic study reported promising outcomes in 11 AIH patients with insufficient response or intolerance to the standard corticosteroid azathioprine combination. Notably, 91% (10/11) achieved biochemical remission, and a significant majority (82%, 9/11) were able to completely discontinue corticosteroid use within a median follow-up of 16 months.[51] Although subsequent case series supported the initial promise of tacrolimus, their findings suggest that its efficacy may not be as strong as initially reported. A large retrospective case series, encompassing 80 AIH patients receiving tacrolimus and 121 receiving MMF, investigated the effectiveness of tacrolimus compared with MMF as second-line therapy. The study demonstrated remarkably similar biochemical response rates between the 2 treatments, 72.5% with tacrolimus and 69.4% with MMF (P=.639).[37] A systematic review of CNI experience in 2022 summarized outcomes of the 58 patients on cyclosporine and 211 patients on tacrolimus previously reported. Both CNIs demonstrated similar remission rates of approximately 59%. Although CNIs had a higher treatment response rate than MMF in primary treatment nonresponders (53%), they were less effective than MMF in AIH patients who were intolerant to first-line treatment (67%). The response rate was markedly higher in second line (52%) than third line (26%). The discontinuation rate owing to side effects was 13% for cyclosporine and 11% for tacrolimus.[52] Although the ERN recommends tacrolimus trough levels of less than 8 ng/mL in adults, target levels are a matter of ongoing debate.[23,50,53] The Dutch AIH Group recently launched the TAILOR study: Tacrolimus Versus Mycophenolate for Autoimmune Hepatitis Patients With Incomplete Response on First-Line Therapy. This phase 3b, multicenter, open-label RCT may further enlighten the ongoing discussions regarding second-line options.[54]

Biologics

Biologics have emerged as potential treatment options for challenging cases of AIH unresponsive to conventional immunosuppressive therapies. Infliximab, the pioneering tumor necrosis factor (TNF)-alpha monoclonal antibody and first widely used biologic therapy, has shown potential in treating challenging cases of AIH. An initial case report in 2009 demonstrated treatment success in an AIH patient unresponsive to multiple immunosuppressive therapies. Subsequently, the same center published the first case series exploring infliximab in difficult-to-treat AIH patients.[55] The study reported a good response rate and a manageable side-effect profile. Notably, 3 infusions of infliximab (5 mg/kg) administered at weeks 0, 2, and 6 led to ALT normalization in 8 of 11 patients and complete biochemical remission in 6 of 11 patients.[56] Although no serious adverse effects were reported, 7 of 11 patients experienced viral or bacterial infections during follow-up. A recent retrospective study of 21 liver centers across 12 countries reported on 42 AIH patients who received infliximab owing to failure of standard, second-line, or third-line therapies, or for extrahepatic autoimmune disease. Complete response was achieved or maintained in 33 patients (78%) during infliximab therapy. Notably, complete response was achieved in 55% of second- or third-line nonresponders and maintained in 16 patients who switched to infliximab for extrahepatic indications.[57] Importantly, experience from rheumatology and inflammatory bowel disease treatment suggests a potential association with hepatotoxicity.[58] Paradoxically, anti-TNF therapy is a well-known cause of DI-ALH and should be used with caution.[7,59]

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen that acts as a B-cell

depleting therapy. Several single case reports have been published, primarily involving AIH accompanying other autoimmune conditions.[60,61] The IAIHG published a retrospective analysis of 22 cases, reporting significant reductions in transaminase and IgG levels starting 1 month after therapy and lasting up to 24 months. Five of these 22 patients experienced flares within a median follow-up of 6 years. No serious adverse events were reported.[62] Recently, the ColHai registry of the Spanish Association for the Study of the Liver published a retrospective analysis of 35 patients with AIH and its variant forms treated with rituximab. The authors reported an 89% (31/35) complete biochemical remission rate and a significant reduction in corticosteroid dose (from a median of 20 mg to 5 mg). Infusion reactions occurred in 9% and infections in 14.3% of patients during follow-up.[63] Notably, 38% of the patients developed flares within 3 years. The induction dose for rituximab is 1000 mg administered via intravenous infusion; however, the optimal maintenance dosing strategy remains unclear. The ColHai registry showed no difference between a fixed dose every 6 months and a CD19-based dose regimen whereby another dose of rituximab is administered when CD19+ B-lymphocyte counts become detectable again.[63] Hepatitis B exposure should be tested prior to treatment initiation for all biologics.

B-cell activating factor (BAFF) is a member of the TNF superfamily and is involved in the survival and maturation of B cells. BAFF blockage via monoclonal antibodies such as belimumab (Benlysta, GSK) or ianalumab also causes B-cell depletion. Belimumab was used as a third-line option in 2 AIH patients refractory to standard therapies. Both patients showed complete biochemical remission and maintained it for 6 months without any adverse events or decompensation.[64] Ianalumab is currently under investigation in AIH patients with an incomplete response or intolerance to standard treatment in a double-blind, randomized, placebo-controlled clinical trial (NCT03217422). The study has announced the completion of enrollment but is still awaiting results.

Conclusion

Despite the core treatment for AIH remaining relatively stable for more than 50 years, significant advancements have refined and improved patient care (Figure 2). MMF has been established as a strong alternative to azathioprine for first-line therapy. Tacrolimus holds promise as a second-line option. Rituximab offers hope for particularly challenging cases, although larger studies are necessary to confirm its efficacy and safety. Infliximab should be used with caution owing to DI-ALH. Additionally, the exploration of novel agents such as anti-BAFF therapy presents exciting possibilities for the future of AIH treatment.

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References

1. Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut*. 2021;70(10):1989-2003.
2. Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. *Lancet*. 2013;382(9902):1433-1444.
3. Hahn JW, Yang HR, Moon JS, et al. Global incidence and prevalence of autoimmune hepatitis, 1970-2022: a systematic review and meta-analysis. *EClinicalMedicine*. 2023;65:102280.
4. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31(5):929-938.
5. Hennes EM, Zeniya M, Czaja AJ, et al; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48(1):169-176.
6. Fujiwara K, Yasui S, Tawada A, Fukuda Y, Nakano M, Yokosuka O. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group criteria in acute-onset autoimmune hepatitis. *Liver Int*. 2011;31(7):1013-1020.
7. Andrade RJ, Aithal GP, de Boer YS, et al; IAIHG and EASL DHILI Consortium. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): an expert opinion meeting report. *J Hepatol*. 2023;79(3):853-866.
8. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology*. 2005;42(1):53-62.
9. Kogan J, Safadi R, Ashur Y, Shouval D, Ilan Y. Prognosis of symptomatic versus asymptomatic autoimmune hepatitis: a study of 68 patients. *J Clin Gastroenterol*. 2002;35(1):75-81.
10. Kanzler S, Löhr H, Gerken G, Galle PR, Lohse AW. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. *Z Gastroenterol*. 2001;39(5):339-341, 344-348.
11. Purnak T, Efe C, Kav T, Wahlin S, Ozaslan E. Treatment response and outcome with two different prednisolone regimens in autoimmune hepatitis. *Dig Dis Sci*. 2017;62(10):2900-2907.
12. Rahim MN, Miquel R, Heneghan MA. Approach to the patient with acute severe autoimmune hepatitis. *JHEP Rep Innov Hepatol*. 2020;2(6):100149.
13. Rahim MN, Liberal R, Miquel R, Heaton ND, Heneghan MA. Acute severe autoimmune hepatitis: corticosteroids or liver transplantation? *Liver Transpl*. 2019;25(6):946-959.
14. Yeoman AD, Westbrook RH, Zen Y, et al. Early predictors of corticosteroid treatment failure in icteric presentations of autoimmune hepatitis. *Hepatology*. 2011;53(3):926-934.
15. Eshraghian A, Taghavi A, Nikeghbalian S. Outcomes of patients with acute severe autoimmune hepatitis: predictors of non-response to corticosteroids and need for liver transplantation. *United European Gastroenterol J*. 2024;12(7):911-918.
16. De Martin E, Coilly A, Chazouillères O, et al; FILFOIE consortium – France. Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: the SURFASA score. *J Hepatol*. 2021;74(6):1325-1334.
17. Mendizabal M, Marciano S, Videla MG, et al. Fulminant presentation of autoimmune hepatitis: clinical features and early predictors of corticosteroid treatment failure. *Eur J Gastroenterol Hepatol*. 2015;27(6):644-648.
18. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology*. 1993;18(4):998-1005.
19. Pape S, Snijders RJALM, Gevers TJG, et al; International Autoimmune Hepatitis Group (IAIHG) collaborators. Systematic review of response criteria and

endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. *J Hepatol*. 2022;76(4):841-849.
20. Candels LS, Rahim MN, Shah S, Heneghan MA. Towards personalised medicine in autoimmune hepatitis: measurement of thiopurine metabolites results in higher biochemical response rates. *J Hepatol*. 2021;75(2):324-332.
21. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1981;1(5):431-435.
22. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol*. 2015;63(4):971-1004.
23. Lohse AW, Sebode M, Jørgensen MH, et al; European Reference Network on Hepatological Diseases (ERN RARE-LIVER); International Autoimmune Hepatitis Group (IAIHG). Second-line and third-line therapy for autoimmune hepatitis: a position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. *J Hepatol*. 2020;73(6):1496-1506.
24. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut*. 1980;21(1):78-83.
25. Pape S, Gevers TJG, Belias M, et al. Predniso(lo)ne dosage and chance of remission in patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol*. 2019;17(10):2068-2075.e2.
26. Manns MP, Woynarowski M, Kreisel W, et al; European AIH-BUC-Study Group. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology*. 2010;139(4):1198-1206.
27. Efe C, Ozaslan E, Kav T, et al. Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome. *Autoimmun Rev*. 2012;11(5):330-334.
28. Díaz-González Á, Hernández-Guerra M, Pérez-Medrano I, et al; ColHai Registry. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. *Hepatology*. 2023;77(4):1095-1105.
29. Soloway RD, Summerskill WH, Baggenstoss AH, 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):820-833.
30. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet*. 1973;1(7806):735-737.
31. Summerskill WH, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut*. 1975;16(11):876-883.
32. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med*. 1995;333(15):958-963.
33. Mack CL, Adams D, Assis DN, 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.
34. Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. *J Hepatol*. 2006;45(4):584-591.
35. Weltzsch JP, Bartel CF, Waldmann M, et al. Optimizing thiopurine therapy in autoimmune hepatitis: a multi-center study on monitoring metabolite profiles and co-therapy with allopurinol. *Hepatology*. 2024;80(5):1026-1040.
36. Özaslan E, Günşar F, Çiftçibaşı Örmeci A, et al. Diagnosis and treatment of autoimmune hepatitis: questions, answers, and illustrative cases: endorsed by Autoimmune Liver Diseases Special Interest Group, Turkish Association for the Study of Liver. *Turk J Gastroenterol*. 2023;34(suppl 2):S1-S33.
37. Chung Y, Ergenc I, Heneghan MA. Optimizing thiopurine therapy in autoimmune hepatitis: a multicenter study on monitoring metabolite profiles and co-therapy with allopurinol. *Hepatology*. 2024;80(5):1000-1002.
38. Hübener S, Oo YH, Than NN, et al. Efficacy of 6-mercaptopurine as second-line treatment for patients with autoimmune hepatitis and azathioprine intolerance. *Clin Gastroenterol Hepatol*. 2016;14(3):445-453.
39. Lees CW, Maan AK, Hansoti B, Satsangi J, Arnott ID. Tolerability and safety of mercaptopurine in azathioprine-intolerant patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2008;27(3):220-227.
40. Devlin SM, Swain MG, Urbanski SJ, Burak KW. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. *Can J Gastroenterol*. 2004;18(5):321-326.
41. Inductivo-Yu I, Adams A, Gish RG, et al. Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol*. 2007;5(7):799-802.
42. Efe C, Hagström H, Ytting H, et al. Efficacy and safety of mycophenolate mofetil and tacrolimus as second-line therapy for patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol*. 2017;15(12):1950-1956.e1.
43. Santiago P, Schwartz I, Tamariz L, Levy C. Systematic review with meta-analysis: mycophenolate mofetil as a second-line therapy for autoimmune hepatitis. *Aliment Pharmacol Ther*. 2019;49(7):830-839.
44. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naïve patients. *J Hepatol*. 2011;55(3):636-646.
45. Zachou K, Gatselis NK, Arvaniti P, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. *Aliment Pharmacol Ther*. 2016;43(10):1035-1047.
46. Dalekos GN, Arvaniti P, Gatselis NK, et al. First results from a propensity matching trial of mycophenolate mofetil vs. azathioprine in treatment-naive AIH patients. *Front Immunol*. 2022;12:798602.
47. Snijders RJALM, Stoelinga AEC, Gevers TJG, et al; Dutch Autoimmune Hepatitis Working Group. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. *J Hepatol*. 2024;80(4):576-585.
48. Pape S, Gevers TJG, Vrolijk JM, et al. High discontinuation rate of azathioprine in autoimmune hepatitis, independent of time of treatment initiation. *Liver Int*. 2020;40(9):2164-2171.
49. Hirunsatitpron P, Hanprasertpong N, Noppakun K, Pruksakorn D, Teekachunhatean S, Koonrungsesomboon N. Mycophenolic acid and cancer risk in solid organ transplant recipients: systematic review and meta-analysis. *Br J Clin Pharmacol*. 2022;88(2):476-489.
50. Wahlin S, Efe C. Both tacrolimus and mycophenylate mophetil should be considered second-line therapy for autoimmune hepatitis. *J Hepatol*. 2021;74(3):753-755.
51. Aqel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. *J Clin Gastroenterol*. 2004;38(9):805-809.
52. Baven-Pronk MA, Hew JM Jr, Biewenga M, et al; Dutch Autoimmune Hepatitis Study Group. Calcineurin inhibitors in the treatment of adult autoimmune hepatitis: a systematic review. *J Clin Transl Hepatol*. 2022;10(6):1155-1166.
53. Liberal R, de Boer YS, Heneghan MA. Established and novel therapeutic options for autoimmune hepatitis. *Lancet Gastroenterol Hepatol*. 2021;6(4):315-326.
54. Stoelinga AEC, Tushuizen ME, van den Hout WB, et al; Dutch Autoimmune Hepatitis Group. Tacrolimus versus mycophenolate for AutoImmune hepatitis patients with incompLete response On first-line therapy (TAILOR study): a study protocol for a phase III, open-label, multicentre, randomised controlled trial. *Trials*. 2024;25(1):61.
55. Weiler-Normann C, Wiegard C, Schramm C, Lohse AW. A case of difficult-to-treat autoimmune hepatitis successfully managed by TNF-alpha blockade. *Am J Gastroenterol*. 2009;104(11):2877-2878.
56. Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol*. 2013;58(3):529-534.
57. Efe C, Lytvyak E, Eşkazan T, et al. Efficacy and safety of infliximab in patients with autoimmune hepatitis [published online September 6, 2024]. *Hepatology*. doi:10.1097/HEP.0000000000001089.
58. Björnsson HK, Gudbjornsson B, Björnsson ES. Infliximab-induced liver injury: clinical phenotypes, autoimmunity and the role of corticosteroid treatment. *J Hepatol*. 2022;76(1):86-92.
59. Borman MA, Urbanski S, Swain MG. Anti-TNF-induced autoimmune hepatitis. *J Hepatol*. 2014;61(1):169-170.
60. Carey EJ, Somaratne K, Rakela J. Successful rituximab therapy in refractory autoimmune hepatitis and Evans syndrome. *Rev Med Chil*. 2011;139(11):1484-1487.
61. Barth E, Clawson J. A case of autoimmune hepatitis treated with rituximab. *Case Rep Gastroenterol*. 2010;4(3):502-509.
62. Than NN, Hodson J, Schmidt-Martin D, et al. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: results from the International Autoimmune Hepatitis Group. *JHEP Rep Innov Hepatol*. 2019;1(6):437-445.
63. Riveiro-Barciela M, Barreira-Díaz A, Esteban P, et al. Rituximab is a safe and effective alternative treatment for patients with autoimmune hepatitis: results from the ColHai registry. *Liver Int*. 2024;44(9):2303-2314.
64. Arvaniti P, Giannoulis G, Gabeta S, Zachou K, Koukoulis GK, Dalekos GN. Belimumab is a promising third-line treatment option for refractory autoimmune hepatitis. *JHEP Rep Innov Hepatol*. 2020;2(4):100123.