Autoimmune hepatitis beyond first-line therapy: management of intolerance and treatment failure

Hepatite autoimune além da primeira linha: manejo da intolerância e da falha terapêutica

Hepatitis autoinmune más allá de la primera línea: manejo de la intolerancia y del fracaso terapêutico

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ABSTRACT
Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease that, if untreated, may progress to advanced fibrosis, cirrhosis, and liver failure. While first-line therapy with corticosteroids and azathioprine (AZA) is standard worldwide, up to 20% of patients develop drug intolerance or fail to achieve complete biochemical remission despite optimized dosing. This mini review summarizes recent evidence for the management of intolerance and non-response in AIH, with focus on distinguishing adverse event–driven drug discontinuation from true pharmacologic failure. We discuss AZA-induced hepatotoxicity, the role of thiopurine metabolite profiling in optimizing therapy, and strategies for identifying preferential methylators. Second-line treatments, including mycophenolate mofetil, 6-mercaptopurine, thioguanine, and calcineurin inhibitors, are reviewed alongside emerging biologics such as rituximab and infliximab. This overview aims to provide clinicians with a concise, evidence-based update on therapeutic alternatives for difficult-to-treat AIH.

Keywords: autoimmune hepatitis, azathioprine, adverse event.

RESUMO
A hepatite autoimune (HAI) é uma doença hepática crônica, imunomediada, que, se não tratada, pode evoluir para fibrose avançada, cirrose e insuficiência hepática. Embora a terapia de primeira linha com corticosteroides e azatioprina (AZA) seja o padrão mundial, até 20% dos pacientes desenvolvem intolerância medicamentosa ou não conseguem alcançar remissão bioquímica completa, mesmo com doses otimizadas. Esta minirrevisão

resume as evidências recentes sobre o manejo da intolerância e da não resposta na HAI, com foco em distinguir a descontinuação do fármaco motivada por eventos adversos do verdadeiro fracasso farmacológico. Discutimos a hepatotoxicidade induzida pela AZA, o papel do monitoramento de metabólitos de tiopurinas na otimização terapêutica e as estratégias para identificar metiladores preferenciais. Tratamentos de segunda linha, incluindo micofenolato de mofetila, 6-mercaptopurina, tioguanina e inibidores de calcineurina, são revisados em paralelo com biológicos emergentes, como rituximabe e infliximabe. Este panorama tem como objetivo oferecer aos clínicos uma atualização concisa e baseada em evidências sobre alternativas terapêuticas para casos de HAI de difícil manejo.

Palavras-chave: hepatite autoimune, azatioprina, evento adverso.

RESUMEN
La hepatitis autoinmune (HAI) es una enfermedad hepática crónica e inmunomediada que, si no se trata, puede progresar a fibrosis avanzada, cirrosis e insuficiencia hepática. Aunque la terapia de primera línea con corticosteroides y azatioprina (AZA) constituye el estándar mundial, hasta un 20% de los pacientes desarrollan intolerancia al fármaco o no logran alcanzar una remisión bioquímica completa a pesar del ajuste óptimo de la dosis. Esta minirrevisión resume la evidencia reciente sobre el manejo de la intolerancia y la falta de respuesta en la HAI, con énfasis en diferenciar la suspensión del fármaco por eventos adversos del verdadero fracaso farmacológico. Se abordan la hepatotoxicidad inducida por AZA, el papel del monitoreo de metabolitos de tiopurinas en la optimización terapéutica y las estrategias para identificar metiladores preferenciales. Los tratamientos de segunda línea, incluidos micofenolato mofetilo, 6-mercaptopurina, tioguanina e inhibidores de la calcineurina, se revisan junto con biológicos emergentes como rituximab e infliximab. Este panorama tiene como objetivo proporcionar a los clínicos una actualización concisa y basada en la evidencia sobre alternativas terapéuticas en los casos de HAI de difícil manejo.

Palabras clave: hepatitis autoinmune, azatioprina, evento adverso.

1 INTRODUCTION

Hepatitis (AIH) is a chronic, immune-mediated inflammatory liver disorder of unknown cause, characterized by a loss of tolerance to hepatocellular antigens in genetically susceptible individuals.[1] The disease exhibits marked heterogeneity, with clinical presentations ranging from incidental biochemical abnormalities to fulminant hepatic failure, and a natural history that—if untreated—often culminates in cirrhosis and end-stage liver disease.[2] Immunopathogenesis is primarily T cell–mediated, with $CD4^+$ lymphocytes orchestrating hepatocyte injury, complemented by B cell–mediated autoantibody production and plasma cell–rich portal inflammation.[1,3] Histological hallmarks include interface hepatitis, frequently accompanied by rosetting of hepatocytes

and lobular inflammation. Serological features typically include elevated serum IgG and the presence of characteristic autoantibodies (ANA, SMA, LKM-1, or highly specific anti-SLA/LP), though IgG elevation may be absent in acute presentations or in elderly patients.[4,5] Diagnosis relies on the integrated assessment of clinical, biochemical, immunological, and histological findings, while systematically excluding competing etiologies of liver injury.[4,5]

The primary therapeutic objective in AIH is to induce and maintain complete biochemical, clinical, and histological remission, thereby halting disease progression, preventing hepatic decompensation, and preserving long-term liver function. This imperative is supported by robust longitudinal data showing that untreated AIH carries a high risk of progression to cirrhosis—often within a decade—and that immunosuppressive therapy improves both transplant-free survival and quality of life. Consequently, treatment is indicated for all patients with active disease, including those with advanced fibrosis or compensated cirrhosis, provided that careful monitoring is implemented to mitigate treatment-related toxicity.[6-9]

Current first-line pharmacologic management is broadly concordant across major guidelines, including the AASLD Practice Guidance, the EASL Clinical Practice Guidelines, and other national societies.[6-8] Standard induction consists of a systemic corticosteroid—prednisone or prednisolone—combined with azathioprine (AZA) in patients without acute liver failure, acute severe hepatitis, or decompensated cirrhosis.[6-8] AZA remains the most widely used antimetabolite; however, recent high-quality evidence, notably the CAMARO trial, demonstrated that mycophenolate mofetil (MMF) combined with corticosteroids achieved higher rates of complete biochemical remission at six months than AZA, with fewer discontinuations and no excess of serious adverse events. Reflecting this, EASL recognizes MMF as an acceptable first-line alternative.[8,10] Prednisone monotherapy remains an option for patients with thiopurine contraindications or intolerance, though long-term use is generally discouraged due to cumulative steroid-related adverse effects.[7,11] Some treatment algorithms introduce AZA only after a short steroid-only lead-in period to confirm responsiveness and exclude early AZA-induced hepatotoxicity.[6] In selected non-cirrhotic patients without acute severe disease, budesonide combined with AZA offers a corticosteroid-sparing alternative, but is contraindicated in cirrhosis and advanced fibrosis due to portosystemic shunting and reduced efficacy.[7,8] Despite these advances, up to 20% of patients fail to achieve sustained remission despite optimized first-line therapy (non-response) or develop treatment-

limiting toxicity (intolerance), most often from AZA-induced hepatotoxicity, myelotoxicity, or corticosteroid-related metabolic complications.[8] These scenarios present a significant clinical challenge and are the focus of this review, which critically examines the evidence base for alternative immunosuppressive regimens, emerging targeted agents, and the integration of pharmacogenetics and therapeutic drug monitoring to optimize outcomes in this difficult-to-treat population.

2 DEFINITION OF TREATMENT FAILURE IN AIH

In the context of AIH, treatment failure refers to worsening laboratory or histological parameters despite full adherence to and optimization of standard therapy. Treatment intolerance, by contrast, denotes inability to maintain therapy due to unacceptable drug-related adverse effects. Accurately distinguishing these entities is essential, as each scenario demands a different therapeutic pathway and has distinct prognostic implications.[7,8] Importantly, before labeling a patient as a non-responder, poor adherence to therapy must be actively excluded, as recent data suggest it is common in AIH and may mimic true pharmacologic failure. In a recent study, nearly half of AIH patients (47%) were found to be non-adherent, a factor strongly associated with reduced rates of biochemical remission. The main drivers included corticosteroid-related cosmetic effects, concurrent use of over-the-counter medications, and anxiety. Unrecognized non-adherence may mimic true pharmacologic failure and prompt unnecessary escalation to second- or third-line immunosuppression.[12]

3 TREATMENT INTOLERANCE

In AIH, treatment intolerance is defined as the occurrence of an adverse event directly attributable to a therapeutic agent that necessitates the permanent discontinuation of that drug. This definition applies to both first-line and subsequent treatment regimens, though it is most frequently encountered with AZA. Corticosteroids, MMF, calcineurin inhibitors, and other immunosuppressants can also be implicated.[7–9] Adverse events prompting cessation include gastrointestinal intolerance, dose-dependent cytopenias, idiosyncratic hepatotoxicity, and, less commonly, severe hypersensitivity reactions. Distinguishing intolerance from non-response is essential, precise recognition of intolerance has direct therapeutic consequences, as it mandates the selection of an

alternative immunosuppressive strategy. The choice is informed by the suspected mechanism of intolerance, the patient's comorbidity profile, and prior drug exposures. Options include MMF, 6-mercaptopurine, thioguanine, or a calcineurin inhibitor, each with its own tolerability spectrum and monitoring requirements. In practice, replacement therapy should be initiated promptly to avoid disease flare, and transition protocols should be individualized to minimize overlapping toxicity and ensure sustained biochemical control.[7,8]

4 AZA-INDUCED HEPATOTOXICITY

AZA-induced hepatotoxicity encompasses a spectrum of liver injuries, ranging from idiosyncratic cholestatic hepatitis to dose-related hepatocellular injury and, in rare cases, vascular lesions such as nodular regenerative hyperplasia.[8,13,14] Although the overall incidence in AIH is relatively low, hepatotoxicity remains one of the most important determinants of early drug discontinuation and transition to second-line therapy. Although the overall incidence in AIH is relatively low, hepatotoxicity remains a major determinant of early drug discontinuation and transition to second-line therapy.[7,8,13] Idiosyncratic reactions typically occur within the first three months of therapy, presenting with fatigue, jaundice, cholestatic biochemical patterns, and, in some cases, eosinophilia or rash. [13,14]

Histopathological findings encompass bland or inflammatory cholestasis, cholangitis-like injury, mixed hepatocellular–cholestatic hepatitis, and, in rare cases, nodular regenerative hyperplasia. The pathogenic mechanisms are incompletely understood and are largely idiosyncratic and dose-independent. Hypersensitivity reactions and metabolic idiosyncrasies related to thiopurine metabolism have been implicated. While thiopurine methyltransferase deficiency is a well-recognized risk factor for myelotoxicity, it does not appear to predispose to hepatotoxicity. Instead, preferential shunting toward excessive production of 6-methylmercaptopurine ribonucleotides (6-MMPR) has been associated with cholestatic injury in some series.[7,13] Additional potential susceptibility factors include advanced age, concomitant hepatotoxic medications, and pre-existing cholestatic or vascular liver disease.[8,15] Onset typically occurs within weeks to months of initiating therapy, although delayed presentations after prolonged exposure are documented. [13,14] In cholestatic injury, alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) rise disproportionately compared to

aminotransferases. Hepatocellular injury is characterized by marked alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations.[7,14] Differentiating drug-induced injury from AIH relapse requires careful temporal correlation with AZA exposure, exclusion of other hepatotoxic causes, and, when indicated, histological reassessment.[7,8]

Given the potential for insidious onset, close biochemical surveillance after AZA initiation is recommended—every 1–2 weeks during the first 4–8 weeks, monthly for the subsequent 3–6 months, and at least quarterly thereafter during maintenance.[7,8] A disproportionate rise in ALP and/or GGT should prompt suspicion of AZA-induced cholestasis, especially if accompanied by pruritus or jaundice.[13,14] Once suspected, AZA should be promptly discontinued to prevent progression to chronic cholestasis or nodular regenerative hyperplasia.[13,14] Biochemical recovery is usually gradual and complete after drug withdrawal, although normalization may take weeks to months.[14] Rechallenge is generally contraindicated due to high recurrence risk.[13] Patients requiring ongoing immunosuppression should transition to alternative agents as will be discussed below.[8,13] Failure to recognize AZA-induced hepatotoxicity may result in unnecessary corticosteroid escalation under the mistaken assumption of treatment non-response, thereby exposing patients to avoidable drug toxicity and disease-related morbidity.[8,14] Early detection and appropriate drug substitution are therefore central to optimizing long-term outcomes in AIH.

5 METABOLISM OF THIOPURINES

5.1 METABOLISM OF THIOPURINES IN AIH

AZA and 6-mercaptopurine (6-MP) remain central components of long-term immunosuppressive therapy in AIH. Once administered, AZA is rapidly converted to 6-MP, which undergoes complex intracellular metabolism yielding active 6-thioguanine nucleotides (6-TGN), methylated metabolites such as 6-MMPR, and inactive degradation products. The balance among these metabolic pathways is determined by enzymatic activities— most notably thiopurine methyltransferase and nucleoside diphosphatase hydrolase 15 (NUDT15)—as well as patient-specific pharmacogenetic and pharmacokinetic factors. Measurement of thiopurine metabolites in red blood cells (RBCs) offers a quantitative approach to assess drug exposure, guide dose adjustments,

and differentiate between therapeutic failure due to underexposure, preferential methylation, or true pharmacologic resistance (figure 1).[7,8,15]

5.2 THIOPURINE METABOLITE MONITORING IN AIH: BALANCING SAFETY AND EFFICACY

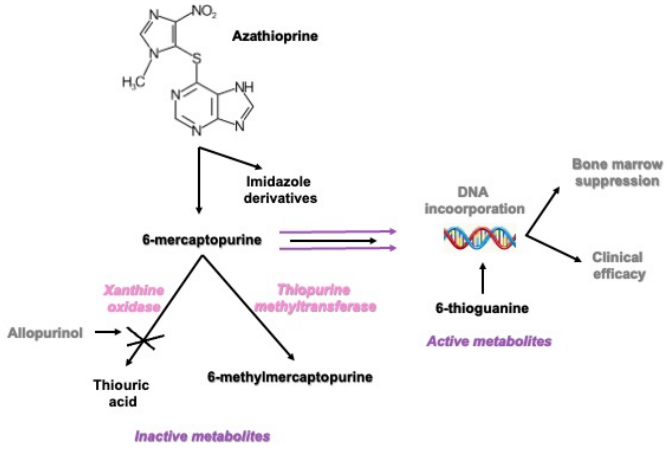
Adverse events from thiopurine therapy in AIH—including myelotoxicity, hepatotoxicity, and gastrointestinal intolerance—are frequently linked to imbalances in metabolite profiles rather than solely to absolute dosing. Elevated 6-TGN concentrations (>450 pmol/8×10^8 RBCs in IBD studies; thresholds in AIH remain less well defined) are associated with an increased risk of myelosuppression, whereas disproportionate accumulation of 6-MMPR (>5,700 pmol/8×10^8 RBCs) correlates with cholestatic hepatotoxicity and, in some cases, nodular regenerative hyperplasia. In "hypermethylators", skewed metabolism favors 6-MMPR production at the expense of 6-TGN, predisposing to toxicity without therapeutic benefit.[8,16,17]

Metabolite testing can therefore identify patients at risk for toxicity before clinically apparent injury develops. In practice, detection of elevated 6-MMPR in the context of hepatotoxicity prompts either dose reduction, the addition of low-dose allopurinol to redirect metabolism toward 6-TGN ("metabolic shunting" strategy), or drug substitution.[14,17,18] Conversely, excessive 6-TGN levels in the setting of cytopenias warrant immediate dose adjustment or discontinuation. Both AASLD and EASL acknowledge the role of metabolite monitoring as a targeted tool, particularly in the setting of adverse events or atypical biochemical responses.[7,8,16]

Metabolite profiling also clarifies incomplete remission. Subtherapeutic 6-TGN levels with low 6-MMPR typically indicate underexposure, either from non-adherence or rapid drug clearance, and may be corrected by dose optimization. Low 6-TGN with high 6-MMPR suggests preferential methylation; in this setting, co-administration of allopurinol with dose reduction of AZA has been shown—particularly in inflammatory bowel disease and increasingly reported in AIH—to improve biochemical remission rates by restoring a favorable 6-TGN/6-MMPR ratio.[15,17] True pharmacologic non-response is characterized by adequate 6-TGN levels with persistent disease activity, indicating the need for therapeutic switch to MMF, calcineurin inhibitors, or other second-line immunosuppressants.[8,17]

While randomized data in AIH remain limited, evidence from large IBD cohorts, observational AIH studies, and recent multicenter experiences suggest that metabolite-guided optimization can improve both efficacy and safety profiles. Integration of metabolite monitoring into AIH management is most impactful in patients with inadequate response to standard dosing, unexplained cytopenias, or biochemical patterns suggestive of hepatotoxicity.[16,17] Table 1 summarizes common thiopurine metabolite patterns (6-TGN and 6-MMPR), their clinical interpretation, and suggested management strategies in AIH.[7,8,15-17]

Figure 1. Thiopurine Metabolite Profiles in Autoimmune Hepatitis



Source: Adapted from Br J Dermatol. 2016;175(Suppl Suppl 2):8–12.[18]

Table 1. Thiopurine Metabolite Profiles and management in Autoimmune Hepatitis

Metabolite Pattern	Clinical Interpretation	Suggested Management
Low 6-TGN, Low 6-MMPR	Underexposure — likely due to non-adherence or rapid clearance	Assess adherence; increase AZA dose if tolerated; repeat levels in 2–4 weeks
Low 6-TGN, High 6-MMPR	Preferential methylation (hypermethylator phenotype) — risk of hepatotoxicity without benefit	Consider low-dose AZA + allopurinol to redirect metabolism; monitor closely for toxicity
High 6-TGN, Normal 6-MMPR	Risk of myelotoxicity	Reduce AZA dose; monitor CBC and metabolites; consider switch if persistent toxicity
Adequate 6-TGN, Persistent disease activity	Pharmacologic non-response	Switch to alternative immunosuppressant
High 6-MMPR with normal 6-TGN	Risk of hepatotoxicity despite adequate active metabolite levels	Reduce AZA dose; consider metabolic shunting with allopurinol; monitor liver enzymes

Source: own elaboration

6 THERAPEUTIC OPTIONS AFTER FAILURE OR INTOLERANCE TO FIRST-LINE THERAPY

A proportion of patients with AIH— estimated between 10% and 20%—fail to achieve complete biochemical remission despite adequate dosing and adherence to standard therapy, or develop treatment-limiting adverse events, most commonly AZA-induced hepatotoxicity, myelotoxicity, or corticosteroid-associated toxicity.[7-9,19] In such cases, prompt transition to alternative immunosuppressive regimens is essential to avoid progressive fibrosis, cirrhosis, or flare related to treatment withdrawal.[7,8] The selection of second-line or rescue therapy is informed by the nature of treatment failure—intolerance versus non-response—as well as patient-specific comorbidities, prior drug exposures, and risk–benefit considerations (Table 2).[7-9,20]

6.1 BUDESONIDE-BASED REGIMENS

Budesonide, a glucocorticoid with high first-pass hepatic metabolism, has been evaluated as an alternative to prednisone in non-cirrhotic AIH, aiming to minimize systemic steroid-related adverse effects. Budesonide combined with AZA has demonstrated non-inferior biochemical remission compared to prednisone–AZA in selected patients, with a lower incidence of corticosteroid-related metabolic adverse effects.[7,8,10] Its use is recommended only in non-cirrhotic patients without acute severe AIH, given its reduced efficacy in advanced fibrosis due to portosystemic shunting.[8] Budesonide has no established role as monotherapy in AZA-intolerant patients and should be discontinued if cirrhosis develops.[7,8] **However, recent real-world data suggest that, even in non-cirrhotic patients, biochemical response rates may be inferior to those achieved with prednisolone (49% vs. 87%), particularly when IgG normalization is included as a treatment target, supporting its use as a niche option rather than a universal first-line alternative.**[21]

7 ALTERNATIVE ANTIMETABOLITES

7.1 6-MERCAPTOPURINE (6-MP)

6-MP is the active metabolite of AZA and can be used in patients intolerant to AZA excipients or to hypersensitivity related to its imidazole moiety.[7,8] Small cohort series in AIH report remission rates comparable to AZA, although cross-toxicity may occur in patients with dose-independent AZA-induced hepatotoxicity.[8,9] Its role is generally confined to cases of immediate-type AZA hypersensitivity, and current evidence does not support its use in patients with severe AZA-induced adverse events such as pancreatitis, myelotoxicity, or cholestatic hepatitis.[21]

7.2 MMF

MMF is the most widely adopted second-line agent in AZA-intolerant or non-responsive AIH.[7,8] Data from multicenter cohorts indicate biochemical remission in approximately 50–80% of AZA-intolerant patients and 25–50% of true non-responders, with better outcomes when used for intolerance rather than refractory disease.[9,19] Adverse effects—chiefly gastrointestinal intolerance and cytopenias—lead to discontinuation in 10–20% of cases. [9,19] As above mentioned, emerging data from randomized trials and long-term observational studies suggest that MMF may also be considered as an initial therapy in carefully selected patients, achieving similar or higher corticosteroid-free biochemical remission compared with AZA, though robust histological follow-up data remain scarce.[21] Brazilian multicenter experience indicates that MMF, often combined with low-dose corticosteroids, achieves biochemical remission in over half of difficult-to-treat cases, but histological remission remains uncommon (≤15%), underscoring the need for prolonged therapy and close monitoring.[22]

7.3 OTHER THIOPURINES

In highly selected patients, thioguanine has been trialed, particularly in “hypermethylators” identified via thiopurine metabolite profiling, although long-term safety data in AIH are limited and concerns about nodular regenerative hyperplasia persist.[8,9]

7.4 CALCINEURIN INHIBITORS (CNIs)

7.4.1 Tacrolimus

Tacrolimus has shown efficacy in inducing remission in patients refractory to AZA and MMF.[7,8] Target trough levels range from 3 to 8 ng/mL, with monitoring for nephrotoxicity, hypertension, and glucose intolerance.[8] Observational studies suggest remission in 50–70% of non-responders, but relapse is common after withdrawal.[8,9] Retrospective series indicate that CNIs may be particularly effective in AZA non-responders compared to MMF, though their use is associated with a higher burden of metabolic and renal adverse effects, justifying their positioning as a third-line option.[21]

7.4.2 Cyclosporine

Cyclosporine has a longer history of use in pediatric AIH and in acute severe presentations, with reported remission rates of 60–80%.[7,8] Its use in adults is limited by metabolic complications, cosmetic adverse effects, and long-term nephrotoxicity. [8,9] Brazilian referral center data confirm that cyclosporine, often combined with AZA and/or prednisone, achieves substantial biochemical improvement in a subset of refractory patients, but treatment discontinuation due to adverse events (gingival hyperplasia, infections, diarrhea) occurs in up to one-third.[22]

7.5 BIOLOGIC AND TARGETED THERAPIES

7.5.1 Anti-CD20 (Rituximab)

Rituximab has been employed as rescue therapy in severe, treatment-refractory AIH, particularly in the context of overlap syndromes or autoimmune cytopenias.[20,23] Case series demonstrate improvements in biochemical parameters and reductions in corticosteroid dependence. Infectious complications and hypogammaglobulinemia warrant caution.[20,23] Recent registry data show biochemical remission in up to 89% of AIH/overlap cases, with a significant reduction in corticosteroid requirements, but flare rates approach 38% within 3 years, highlighting the need for long-term surveillance.[21]

7.5.2 Anti-TNF agents (Infliximab)

Case series describe infliximab use in AIH refractory to multiple immunosuppressants, with some patients achieving partial remission.[23] However, risks include exacerbation of autoimmunity and serious infections; thus, infliximab remains an exceptional, last-resort intervention.[24] Accumulating multicenter experience suggests higher efficacy when infliximab is introduced earlier in the treatment sequence (post–first or second line), whereas third-line use is associated with lower sustained remission rates and higher infection risk. [21]

7.5.3 JAK inhibition (Tofacitinib)

An emerging therapeutic avenue in ultra-refractory AIH involves inhibition of the Janus kinase (JAK) pathway. A recent case report detailed a young female with persistent disease activity despite sequential treatment with prednisolone–AZA, MMF, tacrolimus, and rituximab. Following the development of bronchiolitis obliterans organizing pneumonia and in the absence of further conventional options, tofacitinib was initiated alongside low-dose corticosteroids. Within three months, complete biochemical remission was achieved, with normalization of aminotransferases and IgG.[25] While anecdotal, this observation highlights JAK inhibition as a potential rescue strategy in AIH unresponsive to multiple immunosuppressive classes. Its rapid onset of action and plausible mechanistic rationale warrant further investigation in controlled studies before routine use can be recommended.

7.5.4 Rescue therapy and liver transplantation

Liver transplantation should be considered in patients with acute liver failure unresponsive to medical therapy, progressive decompensated cirrhosis despite optimized immunosuppression, or severe steroid dependence that significantly impairs quality of life[7,8,26] Post-transplant recurrence of AIH occurs in up to 30% of patients, necessitating long-term immunosuppression, often with CNIs and low-dose steroids.[7,8,26] Predictors of post-transplant recurrence include HLA-DR3 positivity, rapid corticosteroid taper post-LT, and prior history of refractory disease; strategies such as maintaining low-dose steroids indefinitely may mitigate recurrence risk.[21]

Table 2. Therapeutic Options After Failure or Intolerance to First-line Therapy in Autoimmune Hepatitis

Agent	Reported Remission Rate	Main Indications	Key Contraindications
Budesonide[10]	Non-inferior to prednisone in CAMARO trial (selected non-cirrhotic patients)	Non-cirrhotic AIH; steroid-sparing	Cirrhosis; acute severe AIH; portosystemic shunting
6-Mercaptopurine (6-MP)[9,19]	Remission rates comparable to AZA in small series	AZA intolerance (imidazole moiety hypersensitivity, excipient reaction)	Cross-toxicity with AZA hepatotoxicity
Mycophenolate mofetil (MMF) [7-9,19]	50–80% in AZA-intolerant; 25–50% in non-responders	AZA intolerance; women of childbearing age; thiopurine contraindication	Significant GI intolerance; cytopenias; teratogenicity
Thioguanine	Limited data; some benefit in hypermethylators	AZA/MMF intolerance; hypermethylator profile	Risk of nodular regenerative hyperplasia
Tacrolimus[8,9]	50–70% in refractory AIH	Refractory to AZA and/or MMF	Nephrotoxicity; hypertension; diabetes
Cyclosporine[7,8]	60–80% in pediatric AIH; some adult benefit	Acute severe AIH; pediatric refractory cases	Nephrotoxicity; metabolic/cosmetic adverse effects
Rituximab[20,23]	Partial to complete remission in select refractory cases	Refractory AIH; overlap syndromes; autoimmune cytopenias	Infection risk; hypogammaglobulinemia
Infliximab[23,24]	Partial remission in last-resort scenarios	Multiple drug failure; overlap with inflammatory bowel disease	Autoimmunity exacerbation; infection
Liver Transplantation[7,8,26]	Excellent survival if performed before advanced multi-organ failure	Acute liver failure; decompensated cirrhosis; steroid dependence with poor QoL	Active uncontrolled infection; severe cardiopulmonary disease

Source: own elaboration

8 CONCLUSION

Management of AIH in patients who are intolerant or non-responsive to conventional therapy remains a complex clinical challenge. Precise differentiation between intolerance and true pharmacologic non-response is critical, as it directly influences therapeutic selection and long-term outcomes. Advances in thiopurine metabolite monitoring and the integration of pharmacogenetic insights now allow for

more individualized and targeted treatment strategies, potentially reducing toxicity while maximizing efficacy.

Second-line options such as MMF, 6-mercaptopurine, thioguanine, and calcineurin inhibitors provide viable alternatives, each with specific indications, limitations, and safety considerations. Biologic agents and targeted therapies, although supported primarily by small series and case reports, offer hope for ultra-refractory cases but require further validation through controlled trials.

In cases of acute liver failure or progressive decompensation despite optimized medical therapy, timely referral for liver transplantation is essential, with post-transplant recurrence risk informing long-term immunosuppressive strategies.

Ultimately, the therapeutic landscape for difficult-to-treat AIH is evolving toward a precision medicine approach—one that balances efficacy, safety, and quality of life. Ongoing research and international collaboration will be fundamental in defining optimal sequencing, monitoring, and combination strategies to improve prognosis in this challenging patient population.

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