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# Advancements in Autoimmune Hepatitis Management: Perspectives for Future Guidelines

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**Abstract**

The first-line treatment for autoimmune hepatitis involves the use of prednisone or prednisolone either as monotherapy or in combination with azathioprine (AZA). Budesonide has shown promise in inducing a complete biochemical response (CBR) with fewer adverse effects and is considered an optional first-line treatment, particularly for patients without cirrhosis; however, it is worth noting that the design of that study favored budesonide. A recent real-life study revealed higher CBR rates with prednisone when equivalent initial doses were administered. Current guidelines recommend mycophenolate mofetil (MMF) for patients who are intolerant to AZA. It is important to mention that the evidence supporting this recommendation is weak, primarily consisting of case series. Nevertheless, MMF has demonstrated superiority to AZA in the context of renal transplant. Recent comparative studies have shown higher CBR rates, lower therapeutic failure rates, and reduced intolerance in the MMF group. These findings may influence future guidelines, potentially leading to a significant modification in the first-line treatment of autoimmune hepatitis. Until recently, the only alternative to corticosteroids was lifelong maintenance treatment with AZA, which comes with notable risks, such as skin cancer and lymphoma. Prospective trials are essential for a more comprehensive assessment of treatment suspension strategies, whether relying on histological criteria, strict biochemical criteria, or a combination of both. Single-center studies using chloroquine diphosphate have shown promising

results in significantly reducing relapse rates compared to placebo. However, these interesting findings have yet to be replicated by other research groups. Additionally, second-line drugs, such as tacrolimus, rituximab, and infliximab, should be subjected to controlled trials for further evaluation.

## INTRODUCTION

Autoimmune hepatitis (AIH) was the first chronic liver disease for which a treatment benefit was demonstrated in randomized studies, marking over 50 years since those pivotal clinical trials. Patients under treatment exhibited a survival rate of 85%-95%, a stark contrast to the 33%-44% observed with a placebo after 2.0 years to 3.5 years of follow-up[1-3].

The first-line treatment of AIH involves the corticosteroid prednisone (PD) or prednisolone, either as monotherapy or in combination with azathioprine (AZA). Corticosteroids readily interfere with the immune system by affecting cytokine production and inhibiting T lymphocyte activation. AZA exerts its immunosuppressive effects by blocking the maturation of lymphocyte precursors, which may take at least 3 mo for the full effect to be accomplished[4].

In 2015, the European Association for the Study of Liver Diseases (EASL) published their practice guidelines on AIH diagnosis and management[5], followed by the American Association for the Study of Liver Diseases (AASLD) in 2019[6] and the Asian Pacific Association for the Study of the Liver in 2021[7]. Both the AASLD and EASL recommend delaying the introduction of AZA for the first 2 wk. This approach, though untested in clinical trials, may aid in distinguishing rare instances of AZA-induced hepatotoxicity from non-response. AZA is primarily employed for its steroid-sparing effect and for maintenance therapy since it is less effective in inducing a response. Once steroid responsiveness is confirmed and thiopurine methyltransferase deficiency is ruled out, AZA can be prescribed, according to these guidelines. Genetic

mutations affecting thiopurine methyltransferase occur in up to 0.6% of the population, but the consequences of using AZA in these individuals can be severe[8].

For over 40 years, this was the standard first-line treatment. Randomized trials involving ursodeoxycholic acid and cyclosporine, as well as intermittent or pulse corticosteroid treatment, yielded negative results[9-13]. In 2010, a clinical trial suggested that budesonide (BD) might be more effective than PD in inducing a response, with the added advantage of causing fewer cosmetic side effects[14]. BD is a glucocorticosteroid with a potent topical effect and a high (> 90%) first-pass uptake[15]. However, this study faced criticism due to the rapid reduction in PD doses, irrespective of biochemical relapse or non-response, reaching 10 mg per day within 8 wk. Importantly, the effectiveness in the control group was much smaller than expected: only 39% in 6 mo. Despite the criticism, the AASLD guidelines recommend BD as a first-line option for patients without cirrhosis, particularly those at risk of adverse corticosteroid-related side effects. Other medical societies take a more cautious approach, suggesting BD as an alternative pending further study.

A recent multicenter real-life study[16] that included treatment-naïve, non-severe AIH patients without cirrhosis revealed that clinicians prescribed BD in only 5% of cases. Notably, BD was more commonly used in patients with significantly lower liver test results (median alanine aminotransferase 198 IU/L *vs* 753 IU/L), with a relative risk of response of 0.20 compared to PD. However, effectiveness was similar in patients with alanine aminotransferase/aspartate aminotransferase levels < 2 times the normal limit. Complete biochemical response was 87% with PD and 51% with BD when equivalent initial doses were used (50 mg PD *vs* 9 mg BD), which was in contrast with the clinical trial favoring budesonide.

Current guidelines recommend mycophenolate mofetil (MMF) only for AZA-intolerant patients. MMF is the prodrug of mycophenolic acid. It exerts an antiproliferative action on lymphocytes by inhibiting inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine synthesis[15]. However, MMF has been found to be superior to AZA in renal transplant protocols, reducing

acute rejection and graft loss[17,18]. Accordingly, two recent studies compared MMF to AZA on a head-to-head basis. The first was a Greek multicenter study published in 2022[19]. It was designed in a way that patients could choose whether to receive AZA (1-2 mg/kg/day up to 150 mg) or MMF (1.5-2.0 mg/day) in addition to a starting PD dose of 40 mg. Notably, the MMF group achieved greater rates of complete biochemical response (96% *vs* 87%) and smaller rates of therapeutic failures (8% *vs* 19%) or treatment modification due to incomplete response or intolerance (11% *vs* 44%) after 4.8 years of follow-up.

Last year in the EASL Liver Meeting, a randomized control trial (the CAMARO trial) was presented[20]. Patients in the AZA arm received a maximum daily dose of 100 mg, while patients in the MMF arm were treated with up to 2000 mg daily, per protocol. In treatment-naïve patients, MMF was superior to AZA for induction of remission (55.3% *vs* 25.8%) with less cessation due to adverse effects (5.1% *vs* 25.8%). Some may argue that the AZA maximum dose was not equivalent to that of MMF, but the magnitude of the difference between the treatment arms was relevant, and an increase of the AZA dose would lead to even greater side effect rates.

After 50 years, an important modification in the first-line treatment of AIH is anticipated, as MMF could be considered an alternative to AZA. Second-line or third-line drugs such as tacrolimus, rituximab, and infliximab need controlled trials for further evaluation, requiring a multicentric effort due to the large sample sizes needed.

Regarding long-term therapy, the prolonged use of corticosteroids is associated with well-established side effects, while maintaining monotherapy with AZA carries risks such as skin cancer and lymphoma[21]. It is recommended to consider a trial of treatment suspension upon achieving a treatment response. However, the suspension of treatment remains a topic of controversy in the management of AIH. Historical data has shown that relapses can lead to the progression of AIH to cirrhosis, liver failure, and even death. Nevertheless, recent publications with closer follow-up have not found these serious complications. A consolidation period of at least 18 mo is recommended, considering that histological remission typically lags behind biochemical remission[6,22].

Plasma cell infiltrates and interface hepatitis have been associated with relapse after treatment[23,24], but those publications defined response as a reduction to less than twice the upper limit of liver tests. It was later demonstrated that complete biochemical normalization, including aminotransferases and gamma globulin levels, correlated with more favorable clinical outcomes. Unfortunately, even using these criteria, relapses still occurred in 46%-81% of patients after 3 years of follow-up[25,26]. However, these publications evaluating relapse risk are potentially biased because of their retrospective nature. Indeed, there is currently no controlled trial to support any treatment withdrawal strategy. A prospective trial in this regard would be invaluable, but it would need to be multicentric to include a sufficient sample size. There is a need to evaluate prospectively whether a liver biopsy is needed before treatment suspension, or if strict biochemical criteria alone are sufficient.

Encouraging results have emerged from single-center studies involving the use of chloroquine diphosphate, demonstrating a significant reduction in relapse rates compared to a placebo. Chloroquine plays an established role in the treatment of autoimmune rheumatic diseases, potentially by interfering with lysosomal phagocytic function, antigen presentation, cytokine production, and other immunoregulatory effects. However, it is important to note that these intriguing findings have yet to be independently replicated by other research groups[27-29].

Promising therapeutic agents, such as those acting on cytokine, chemokine, and signaling pathways, cell-based therapy, microbiome modulation, or nanomedicine, are still in the early stages of research[30].

## CONCLUSION

The clinical management of autoimmune hepatitis is primarily rooted in landmark clinical trials conducted over 50 years ago. While certain aspects of this management have evolved, recent research has provided data that hold the potential to refine our current guidelines. Nonetheless, achieving optimal strategies for response induction, treatment maintenance, and suspension will require ongoing research and efforts.

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