ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Azathioprine or Mycophenolate Mofetil: Which Should Be Used in Patients With Autoimmune Hepatitis?

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G&H How effective and safe is the use of azathioprine in patients with autoimmune hepatitis?

AB Autoimmune hepatitis is a chronic inflammatory liver disorder characterized by immune-mediated destruction of hepatocytes, leading to fibrosis, cirrhosis, and liver failure if left untreated. The management of autoimmune hepatitis has evolved significantly over the years, with current guidelines from both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver recommending azathioprine as a first-line therapy in combination with corticosteroids. Azathioprine, an immunosuppressive agent, has demonstrated remarkable efficacy in achieving biochemical remission, with close to 70% of patients attaining normalized alanine aminotransferase (ALT) and immunoglobulin G (IgG) levels—the hallmark of biochemical remission. This is a critical endpoint in autoimmune hepatitis management, as sustained remission reduces the risk of disease progression, liver fibrosis, and the need for liver transplantation.

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Although azathioprine is generally considered to be safe and well tolerated, it is associated with a range of potential side effects, some of which require careful monitoring. The most common adverse effect is pancytopenia, a condition characterized by a reduction in red blood cells, white blood cells, and platelets.

Skin hypersensitivity reactions, including rash and photosensitivity, are other notable side effects of azathioprine. These reactions are typically mild but can occasionally progress to more severe dermatologic conditions. Patients should be advised to use sun protection and report any skin changes promptly.

An unusual but serious side effect of azathioprine is pancreatitis, which presents as acute abdominal pain, nausea, and vomiting. Although rare, pancreatitis can be life-threatening and requires immediate discontinuation of the drug and appropriate medical management. The exact mechanism linking azathioprine to pancreatitis remains unclear, but it is thought to involve an idiosyncratic reaction.

G&H What research has examined the use of mycophenolate mofetil in patients with autoimmune hepatitis?

AB For decades, azathioprine in combination with corticosteroids has been the cornerstone of autoimmune hepatitis treatment, with guidelines endorsing this strategy

for first-line treatment. However, evidence from a propensity matching study by Dalekos and colleagues in 2022 in Greece highlighted the potential of mycophenolate mofetil as a superior alternative to azathioprine. More recently, a Dutch randomized controlled trial by Snijders and colleagues also supported mycophenolate mofetil's role in autoimmune hepatitis management. In this trial, which randomized patients to either mycophenolate mofetil plus corticosteroids or azathioprine plus corticosteroids, those in the first group demonstrated significantly better outcomes in terms of biochemical remission rates. Patients treated with mycophenolate mofetil were more likely to achieve normalized ALT and IgG levels, underscoring its efficacy as a first-line therapy. Importantly, mycophenolate mofetil was also associated with a lower incidence of adverse effects. Thus, these studies have demonstrated that mycophenolate mofetil is associated with higher rates of biochemical remission, fewer side effects, and better patient compliance compared with traditional azathioprine and prednisone regimens.

The safety profile of mycophenolate mofetil is particularly noteworthy. Unlike azathioprine, which carries a risk of myelosuppression and pancreatitis, mycophenolate mofetil is generally better tolerated, with gastrointestinal symptoms being the most commonly reported side effects. Its favorable safety profile, coupled with its superior efficacy, makes mycophenolate mofetil an attractive option for patients with autoimmune hepatitis, especially those intolerant to azathioprine or at higher risk of its adverse effects.

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G&H What limitations should be kept in mind when viewing these study findings?

AB Although the evidence supporting use of mycophenolate mofetil in autoimmune hepatitis is promising, it is essential to critically evaluate the limitations of the studies that have shaped this narrative. The duration of the Dutch randomized controlled trial was only 6 months, which is relatively short for a chronic disease such as autoimmune hepatitis. Long-term outcomes, including sustained remission, progression to cirrhosis, and safety profiles over extended periods, could not be assessed. A longer follow-up would provide more robust evidence regarding mycophenolate mofetil's efficacy and safety in the management of patients with autoimmune hepatitis. The Greek study that demonstrated better biochemical remission rates with mycophenolate mofetil compared with azathioprine was retrospective. Retrospective studies are inherently prone to biases.

G&H What has been your experience using these agents in patients with autoimmune hepatitis?

AB I have seen these study findings reflected in my own practice. I have changed my practice and now prescribe mycophenolate mofetil for patients with autoimmune hepatitis as much as I can. However, mycophenolate mofetil should not be used in all patients with autoimmune hepatitis. This disease predominantly occurs in females of reproductive age, so caution is needed, as mycophenolate mofetil is contraindicated during pregnancy. Providers should have a discussion about using mycophenolate mofetil. When I treat females of reproductive age who are thinking about becoming pregnant, I usually prescribe azathioprine because safety data have shown that azathioprine is safe in pregnancy and does not cause any harm to the fetus. If a patient is older or not considering pregnancy, then I usually start with mycophenolate mofetil.

G&H What other considerations should be kept in mind when selecting a treatment for autoimmune hepatitis?

AB Mycophenolate mofetil also has a number of side effects. The gastrointestinal side effects are quite striking. Up to 40% of patients can develop nausea, vomiting, and diarrhea, and patients can develop colitis-type injury. Some patients can also develop severe pancytopenias. Overall, there is no good algorithm to guide which therapy should be used first, so it is important to look at the patient's profile and discuss with the patient how to balance all of the risks and benefits of long-term use and decide on the best treatment option. Treatment selection also involves considering the patient's comorbidities, other medications, and potential drug-drug interactions, as well as the sex and age of the patient, as discussed.

If the patient does not achieve biochemical response 6 to 12 months after starting treatment, then a second-line therapy such as tacrolimus should be considered.

G&H In patients who are likely to need a liver transplant, how aggressive should a provider be in trying to improve their autoimmune hepatitis?

AB When patients are very sick and their bilirubin level and Model for End-Stage Liver Disease score are elevated, the use of mycophenolate mofetil and azathioprine can make matters worse. If I know that patients are going to undergo liver transplant, I do not use these medications. The risks of side effects are much higher in individuals with decompensated liver disease. I usually evaluate these patients for liver transplant, making sure that they are appropriate transplant candidates, and place them on the transplant waiting list as soon as I can. Data have shown that patients with decompensated liver disease who start immunosuppressive therapy are at increased risk for side effects as well as life-threating infections that could potentially prevent these patients from being listed for liver transplant.

G&H What further research is needed?

AB We need data on treatment for longer than 24 weeks as well as data on more patients than just those who are treatment-naive. We need to study patients with refractory disease and patients who are nonresponders, and we need to do so in clinical trials. Autoimmune hepatitis is a rare disease, which makes research and patient enrollment complex, but obtaining long-term data will help the community determine whether our guidelines need to be changed.

Disclosures

Dr Bonder has done consulting for Intercept Pharmaceuticals, Zydus Therapeutics, Chemomab, CymaBay Therapeutics, Mirum Pharmaceuticals, Gilead Sciences, and Cara; received royalties or holding licenses from UpToDate and DynaMed; worked with the AASLD Editorial Board for Clinical Liver Disease; and provided expert testimony for Expert Review.

Suggested Reading

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.

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.

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.

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.

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.

Zachou K, Gatselis NK, 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.