

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Long-Term Use of Azathioprine in the Management of Autoimmune Hepatitis



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### G&H How effective are the first- and second-line treatment options for autoimmune hepatitis?

**MP** First-line treatment consists of corticosteroids with azathioprine. A number of randomized, controlled trials have shown that this combination is efficacious in 80% to 90% of patients. Approximately a decade ago, research showed that budesonide and prednisone were equally efficacious for first-line treatment with azathioprine. However, budesonide has fewer side effects because it has a high first-pass metabolism with minimal systemic absorption. This means that the rest of the body has less corticosteroid exposure and, thus, fewer side effects.

Second-line treatment includes mycophenolate mofetil (CellCept, Genentech) instead of azathioprine. However, there has never been a randomized, controlled trial of this treatment approach in autoimmune hepatitis. Other drugs, such as calcineurin inhibitors, have also been used. There was one small randomized, controlled trial of tacrolimus that was used in patients who failed first-line therapies. However, salvage therapies have a lower efficacy. Tumor necrosis factor inhibitors and anti-CD20 agents such as rituximab (Rituxan, Genentech) have also been used in small case series.

### G&H Is long-term treatment always required for this disease?

**MP** It is nearly always required. Patients who have excellent disease control for 2 years or more and have no inflammation on biopsy can undergo a trial of stopping

immunosuppression, but in over half of the patients, the disease will recur. One study showed that if the patient's serum immunoglobulin (Ig) G level did not drop below 1200 mg/dL and the alanine aminotransferase (ALT) level was not normal (19 U/L for women and 30 U/L for men) while the patient was receiving treatment, then relapse always occurred once treatment was stopped. If those measures were met for at least 2 years while the patient was on treatment, there was a 50% chance of relapse after treatment discontinuation. Thus, long-term therapy is required in the majority of cases.

### G&H How significant is the risk of squamous cell carcinoma with long-term use of azathioprine?

**MP** Nonmelanoma skin cancer, which includes basal cell and squamous cell cancer, is well described as a complication of azathioprine, an immunosuppressant. Nonmelanoma skin cancer is a serious side effect that varies depending on the disease and the doses used. Thus, all patients on azathioprine should undergo yearly skin checks by a dermatologist.

A study of patients with rheumatologic diseases on a mean dose of azathioprine of over 100 mg per day found an increased incidence of squamous cell carcinoma, which rose with time on therapy and was higher in older patients. These findings have been validated in other studies. The largest data come from the transplantation literature, particularly kidney transplantation, where azathioprine was used with prednisone. Nonmelanoma skin cancer was quite common. A study of autoimmune inflammatory

rheumatologic diseases found nonmelanoma skin cancer in 7% of patients, but these patients were receiving 2 mg/kg/day, which is higher than the dose typically used in autoimmune hepatitis.

**G&H** Has there been any research specifically on this and other side effects in the setting of autoimmune hepatitis?

**MP** Yes. Side effects from azathioprine occur in 10% to 20% of autoimmune hepatitis patients and include non-melanoma skin cancer, pancreatitis, nausea and vomiting, abnormal liver function test results, and bone marrow suppression. There have been many studies on the safety of azathioprine. An article by Dr Benedetta Terziroli Beretta-Piccoli and colleagues, published in the *World Journal of Gastroenterology* in 2017, provides a balanced discussion of all of the different treatment choices and studies, not just in autoimmune hepatitis, but in rheumatologic diseases and inflammatory bowel disease.

**G&H** Is the likelihood of squamous cell carcinoma increased in certain subgroups of patients on azathioprine?

**MP** Yes, the likelihood of nonmelanoma skin cancer is increased with higher doses, longer-term therapy, and older age. It is also higher in patients predisposed to nonmelanoma skin cancer, such as those with high sun exposure, artificial tanning, and fair skin.

**G&H** What might explain the increased incidence of squamous cell carcinoma with long-term use of azathioprine?

**MP** Azathioprine antagonizes purine metabolism, thus interfering with DNA and leading to cytotoxicity. The resulting abnormal DNA is thought to lead to cancer. In addition, azathioprine is a carcinogen with antiproliferative effects. Whether its effect on neoplasia is due to a direct action, the amount of other immunosuppression used, or an increased sensitivity to ultraviolet exposure is not clear. Solid organ transplant recipients and patients with inflammatory bowel disease have an increased risk of both nonmelanoma skin cancer and non-Hodgkin lymphoma. Non-Hodgkin lymphoma is less common in autoimmune hepatitis but whether this is due to the lower doses utilized or other factors is not known.

**G&H** If squamous cell carcinoma does develop, should azathioprine be discontinued?

**MP** Yes, and that is also the case if basal cell cancer develops, because alternative treatments are available. In

the past, only prednisone and azathioprine were available. Now autoimmune hepatitis can be treated with prednisone, budesonide, azathioprine, and mycophenolate mofetil.

**G&H** Overall, how safe is long-term use of azathioprine in patients with autoimmune hepatitis?

**MP** Autoimmune hepatitis is a life-threatening disease, and all of the treatment options have some side effects. This is important to keep in mind when considering the safety of azathioprine. Prednisone has significant side effects—increased weight, diabetes, metabolic syndrome, obesity, increased risk of infection, and hypertension—which are, in my opinion, equally as life-threatening as nonmelanoma skin cancer. The major side effect of mycophenolate mofetil in young patients is teratogenicity. Therefore, it cannot be used in pregnancy, and patients must be told that if they are thinking about becoming pregnant, they have to switch off the drug before becoming pregnant. Mycophenolate mofetil can also cause bone marrow suppression and gastrointestinal upset. Budesonide, which is the newest treatment option, has very few side effects because of its first-pass effect in the liver. However, this drug is contraindicated in cirrhotic patients—who account for 40% of autoimmune hepatitis patients on first presentation—because the first pass does not occur due to shunting in the liver. Calcineurin inhibitors have a large number of side effects, including high blood pressure, tremors, renal disease, and high potassium. Patients on these therapies need to be monitored extremely closely.

I do not consider azathioprine any more toxic than prednisone or mycophenolate mofetil, and I certainly consider it less toxic than calcineurin inhibitors. However, budesonide is clearly less toxic. In the past, azathioprine was commonly used long term to spare patients from the side effects of prednisone, but it would be interesting to see whether budesonide without azathioprine could be used for long-term management of noncirrhotic patients with autoimmune hepatitis. The dose of budesonide could be decreased over time. A few of my autoimmune hepatitis patients are on budesonide monotherapy, but this treatment approach has never been studied in a randomized, controlled fashion. This approach could only be studied in noncirrhotic patients and might avoid the side effects of azathioprine, prednisone, and mycophenolate mofetil.

**G&H** Currently, how are these treatments chosen for autoimmune hepatitis patients?

**MP** Usually, if patients are not cirrhotic, they can be treated with budesonide and azathioprine. If they are cirrhotic, they are treated with prednisone and azathioprine.

If they do not tolerate azathioprine because of toxicity, mycophenolate mofetil is usually the next line of therapy. If they do not tolerate budesonide and the disease is not well controlled, prednisone is used. If patients have very acute autoimmune hepatitis, they are often started on high-dose prednisone and, when their ALT level drops below 100 U/L, they can be switched to budesonide 3 mg three times daily along with azathioprine.

### G&H What other considerations should be kept in mind when managing patients on long-term azathioprine therapy?

**MP** Before starting azathioprine therapy, the thiopurine methyltransferase (TPMT) level should be tested. If it is normal, the patient will be able to tolerate standard doses of azathioprine and should be monitored every 3 months with complete blood counts to ensure that there is no bone marrow suppression. Lower doses of azathioprine should be used if the TPMT level is intermediate, and if the level is low, other therapies should be tried. As mentioned, a yearly skin check is needed to diagnose and manage nonmelanoma skin cancer. Patients on azathioprine are immunosuppressed, so they are at a higher risk of infections. Autoimmune hepatitis itself is an immune-mediated disease, which may put patients at a higher risk. Lymphoma has been described, but usually in patients taking higher than 2 mg/kg/day and in the setting of inflammatory bowel disease and transplantation.

### G&H What is the optimal dosage of azathioprine for the treatment of autoimmune hepatitis?

**MP** The dose is usually 1.0 to 1.5 mg/kg/day in the early stages, but can then be decreased depending on the patient's ALT and IgG levels. It is important to monitor the IgG level closely because when it drops and is in the normal range with a normal ALT level, the azathioprine dose can be decreased. I have many patients on 50 or even 25 mg of azathioprine per day, which seems to be less toxic.

### G&H When patients are in remission, how should they be treated?

**MP** Once patients on prednisone and azathioprine are in remission, the prednisone should be decreased first and then stopped, and then over months, the azathioprine should be slowly decreased. If patients are on mycophenolate mofetil and prednisone, the same should be done. If budesonide is used, the dosage should be decreased by 1 pill (3 mg) every few months if IgG and ALT levels are normal. The rate of decrease in immunosuppressants depends upon the rate at which the patient went into remission. The faster the patient took to achieve

remission, the more likely that the immunosuppressant drug doses can be decreased in remission. If more time was required to achieve remission, it is likely that the immunosuppressant drug doses will need to be decreased more slowly during remission. Often, practitioners decrease doses too rapidly, which can lead to a flare in autoimmune hepatitis. Patience is required to wait until the ALT level is near normal and the IgG level is in or near the normal range before doses are decreased. Going slower means patients end up receiving less immunosuppressant medication in the long term, which is a benefit.

It is very important that practitioners monitor patients in remission closely to avoid any risks and complications. A number of my patients have been on high-dose prednisone over long periods of time and have developed metabolic syndrome and nonalcoholic fatty liver disease. If a patient has a flare in his or her ALT level but the IgG level is normal, I would be suspicious of nonalcoholic fatty liver disease, and liver biopsy is required to determine whether it represents a flare in autoimmune hepatitis or the development of nonalcoholic fatty liver disease, which require different therapies.

### G&H How else should autoimmune hepatitis patients be followed long term?

**MP** Once they are in remission, they should be followed with 3 monthly liver function tests, complete blood counts, and IgG monitoring. As mentioned, they should undergo a yearly skin check for nonmelanoma skin cancer. They should also undergo bone density testing, which, if abnormal, should be treated and monitored. In addition, patients should have their 25-hydroxyvitamin D levels checked yearly and treated as appropriate.

### G&H Should azathioprine be avoided in any patients?

**MP** It should not be given to patients who already had nonmelanoma skin cancer or who have a very low TPMT level because alternative therapies are available.

*Dr Peters has no relevant conflicts of interest to disclose.*

### Suggested Reading

Sebode M, Hartl J, Vergani D, Lohse AW; International Autoimmune Hepatitis Group (IAIHG). Autoimmune hepatitis: from current knowledge and clinical practice to future research agenda. *Liver Int.* 2018;38(1):15-22.

Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. *World J Gastroenterol.* 2017;23(33):6030-6048.

van den Reek JM, van Lümig PP, Janssen M, et al. Increased incidence of squamous cell carcinoma of the skin after long-term treatment with azathioprine in patients with auto-immune inflammatory rheumatic diseases. *J Eur Acad Dermatol Venereol.* 2014;28(1):27-33.