Immunosuppression in Autoimmune Hepatitis: Is There an End Game?

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INTRODUCTION

Autoimmune hepatitis (AIH) is a rare, chronic disease associated with the development of cirrhosis and premature mortality. Current guidelines state that patients with AIH should receive induction therapy with corticosteroids or the combination of corticosteroids/azathioprine, followed by maintenance therapy with lower doses of steroids and/or azathioprine (1–3). However, the optimal strategy for the ongoing treatment beyond this point remains unclear.

The critical decision becomes, should immunosuppression therapy be continued or withdrawn? On the one hand, liver-related complications and mortality in AIH are strongly associated with the frequency of flares and immunosuppression therapy has been shown to decrease relapse rates (4). Conversely, the long-term risks of immunosuppression can be substantial, particularly for young patients with AIH faced with the prospect of decades of treatment (5).

The high relapse rate and variability in clinical guidelines may complicate the decision and execution of immunosuppression withdrawal in AIH (Table 1). In this review, we provide an overview on the existing literature on stopping of AIH therapy and propose an algorithm for withdrawal of immunosuppression in AIH.

RATIONALE FOR WITHDRAWING IMMUNOSUPPRESSION

Uncertain benefits of maintenance immunosuppression

The benefits of induction therapy for AIH have been demonstrated by multiple randomized controlled trials showing that prednisone monotherapy or combination prednisone and azathioprine therapy effectively induces remission and decreases mortality (4). There have also been some investigations on alternative AIH therapies including mycophenolate mofetil, cyclosporine, tacrolimus, tumor necrosis factor inhibitors, and ursodeoxycholic acid. Currently, these options should be considered second or third line therapies (2,6).

However, there are less data supporting the benefits of maintenance therapy. There are 2 randomized trials examining azathioprine monotherapy or combination azathioprine/prednisone therapy including a total of 97 patients demonstrating high rates of remission in treated groups (4). The lack of deaths in these studies precluded the assessment of the effect of maintenance therapy on mortality. Given that relapses are associated with liver-related complications and deaths, it has been deduced that maintenance therapy reduces the risk of liver-related death or transplantation in AIH, but this has never been conclusively demonstrated (4).

Medication-related side effects

Corticosteroid-related side effects include cosmetic changes (e.g., weight gain, acne, hirsutism, and facial rounding), glucose intolerance, osteoporosis, and lower health-related quality of life (5,7). Budesonide therapy may reduce steroid-related side effects, but it cannot be used in patients with cirrhosis and has less established long-term efficacy data than prednisone/prednisolone (2).

Azathioprine can cause mild myelosuppression, nausea, rash, and fever (5). More severe but less common toxicities include severe cytopenias, pancreatitis, and hepatotoxicity. Finally, azathioprine has been linked with an increased risk of malignancy, including skin cancer and lymphoma. Although the absolute increase in the risk of malignancy from azathioprine is small, this association is particularly concerning for young patients faced with the prospect of multiple decades of treatment.

PROPOSED STRATEGY FOR IDENTIFYING DRUG WITHDRAWAL CANDIDATES

Given the uncertain benefits and known harms of long-term immunosuppression, withdrawal should be considered for many patients with AIH. However, adequate patient selection is vital, given the high frequency and potential dangers of relapse. This is particularly true for the relatively high proportion of patients with AIH with cirrhosis at baseline, for whom a relapse could be deadly. Therefore, it is important to assess the patient's risk of relapse and ability to sustain another relapse before considering drug withdrawal.

Before considering immunosuppression withdrawal, it is important to consider whether the patient may have a variant form of AIH, with overlapping clinical, serological, or histological characteristics of primary sclerosing cholangitis or primary biliary cholangitis (2). Data on relapse rates and treatment response in AIH may not be generalizable to these patients. Furthermore, a patient's liver transplant candidacy should be considered before

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Table 1. Treatment guidelines for immunosuppression withdrawal in autoimmune hepatitis

	Minimum criteria for drug withdrawal	Tapering recommendations	Lab monitoring during and after drug withdrawal
AASLD (1)	Normal AST or ALT,[a] total bilirubin, gamma-globulin or IgG level, and normal liver histology not exhibiting inflammatory activity. Treatment should be continued for at least 24 mo after achieving biochemical remission.	Gradual prednisone taper over a 6-wk period.	AST or ALT, total bilirubin, and gamma-globulin levels at 3 wk intervals during and for 3 mo after drug withdrawal. Repeat laboratory assessments thereafter every 6 mo for at least 1 yr and then every year lifelong.
EASL (2)	Normal IgG and transaminases without histological disease activity (HAI < 4). Treatment should be continued for at least 3 yr and for at least 2 yr after biochemical normalization.	Stepwise reduction of immunosuppressive agents. No further specifications.	Patients should be closely monitored immediately after treatment withdrawal and have lifelong surveillance. No further specifications.
BSG (3)	Normal transaminases and histologic remission. Treatment should be continued for at least 2 yr and for at least 12 mo after normalization of transaminases.	Gradual prednisone taper of 2.5 mg/d each month.	Monitoring of liver tests. No further specifications.

AASLD, American Association for the Study of Liver Diseases; BSG, British Society of Gastroenterology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASL, the European Association for the Study of the Liver; HAI, hepatitis activity index; IgG, immunoglobulin G.
[a]Normal ALT <25 for females and <33 for males (17).

initiating immunosuppression withdrawal, given that relapse may increase the risk of liver failure (8).

How likely is a relapse in my patient?

There are several factors that clearly affect relapse risk (Figure 1) (9). First, drug-induced AIH (DIAIH), most often related to minocycline or nitrofurantoin use, portends a good prognosis. DIAIH has biochemical and histologic features closely resembling nondrug-related AIH but does not typically relapse after immunosuppression is withdrawn if the culprit medication is avoided (10).

Second, longer duration of therapy and shorter time to achieve remission are associated with lower rates of relapse (4). In 1 large series, patients with more than 4 years of continuous therapy had a 67% probability of sustained response compared with 17% among those treated for 2–4 years (11). In another study, relapse occurred after medication withdrawal in nearly 90% of patients who failed to achieve remission within 5 months (12).

Third, and perhaps the most important, those who demonstrate biochemical and histologic remission before treatment withdrawal are at lower risk for relapse compared with those who have either had an incomplete response or treatment failure (1). Normal liver enzymes and immunoglobulin G (IgG) levels are necessary but potentially insufficient for confirming remission. Over half of patients with normal biochemical testing will still have evidence of interface hepatitis (1). Histologic remission therefore remains an important treatment endpoint (12,13).

There are a number of other potential predictors of relapse risk outlined in Figure 1 including psychological stress, patient age, and coexisting autoimmune disease. In addition to autoantibody

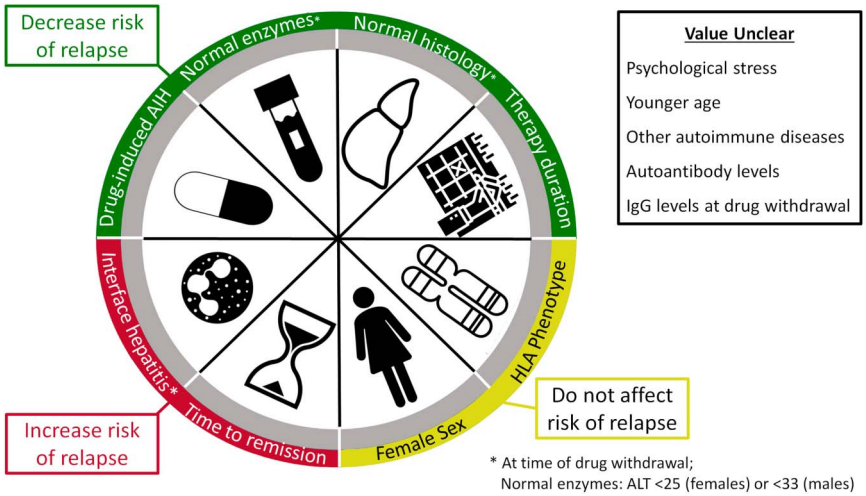

Figure 1. Prognostic factors in assessing the risk of relapse after drug withdrawal in AIH. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G. Normal ranges for liver enzymes were obtained from the ACG Clinical Guideline for Evaluation of Abnormal Liver Chemistries (17).

and IgG levels, there are novel noninvasive markers that show promise in predicting treatment failure, including increased mean platelet volume and hypoalbuminemia (14). However, the role of noninvasive markers for the assessment of disease and response to therapy is controversial and continues to evolve. Finally, given that AIH epidemiology and phenotype differ according to ethnicity, there may be additional genetic, etiological, or socioeconomic factors that influence disease course and relapse risk (2).

Is my patient healthy enough to experience a relapse?

Each relapse requires reinitiation of induction dose corticosteroids, which has several potential downstream consequences. Therefore, providers should proceed with caution when considering drug withdrawal in patients at increased risk for significant corticosteroid-related side effects. Such patient populations include those with osteoporosis or signs of metabolic syndrome, given that corticosteroids can reduce bone density and predispose to obesity, glucose intolerance, hypertension, and hyperlipidemia (5). Furthermore, withdrawal must be judiciously approached in those with underlying psychiatric comorbidities or emotional lability because steroid use has been correlated with anxiety and depression (7).

Patients who relapse often achieve remission with reinstitution of azathioprine and induction dose steroids, but each additional relapse increases the risk of fibrosis, liver-related complications, and death (8). The risk of significant fibrosis and liver-related complications increases significantly after a third relapse and poor outcomes occur almost exclusively in those with established cirrhosis (8,9). Therefore, drug withdrawal should be avoided in those with a previous relapse or evidence of significant fibrosis/cirrhosis.

SUGGESTED APPROACH TO TREATMENT WITHDRAWAL

A closely monitored treatment withdrawal should be considered in patients with at least 2 years of therapy, no previous relapses, no clinical/biochemical/histologic evidence of ongoing inflammation or significant fibrosis and low risk of corticosteroid-related side effects (Figure 2). If the decision is made to withdraw therapy, there are no clear guidelines for how to safely taper medications. If patients are on prednisone monotherapy, a slow taper of 2.5 mg/d/mo can be followed (1,3). For patients on azathioprine, some clinicians stop therapy completely while others wean the dose gradually.

Although there is no clear consensus on how to taper therapy, there are clear recommendations for monitoring patients after drug withdrawal (1–3). Liver function and IgG testing should be performed every 3 weeks during the tapering phase and for at least 3 months after stopping therapy. Thereafter, laboratory monitoring should occur every 3 months for up to a year. If the biochemical markers remain normal, they should be checked every 6 months for 2–3 years, followed by annually. Periodic noninvasive fibrosis assessment (e.g., transient elastography) may also be considered (15). Although relapses tend to occur within the first year after discontinuation, monitoring should continue indefinitely because disease relapse can happen at any time (16).

CONCLUSION

In conclusion, AIH is a serious, lifelong disease that can cause liver-related morbidity and mortality. Patients can achieve

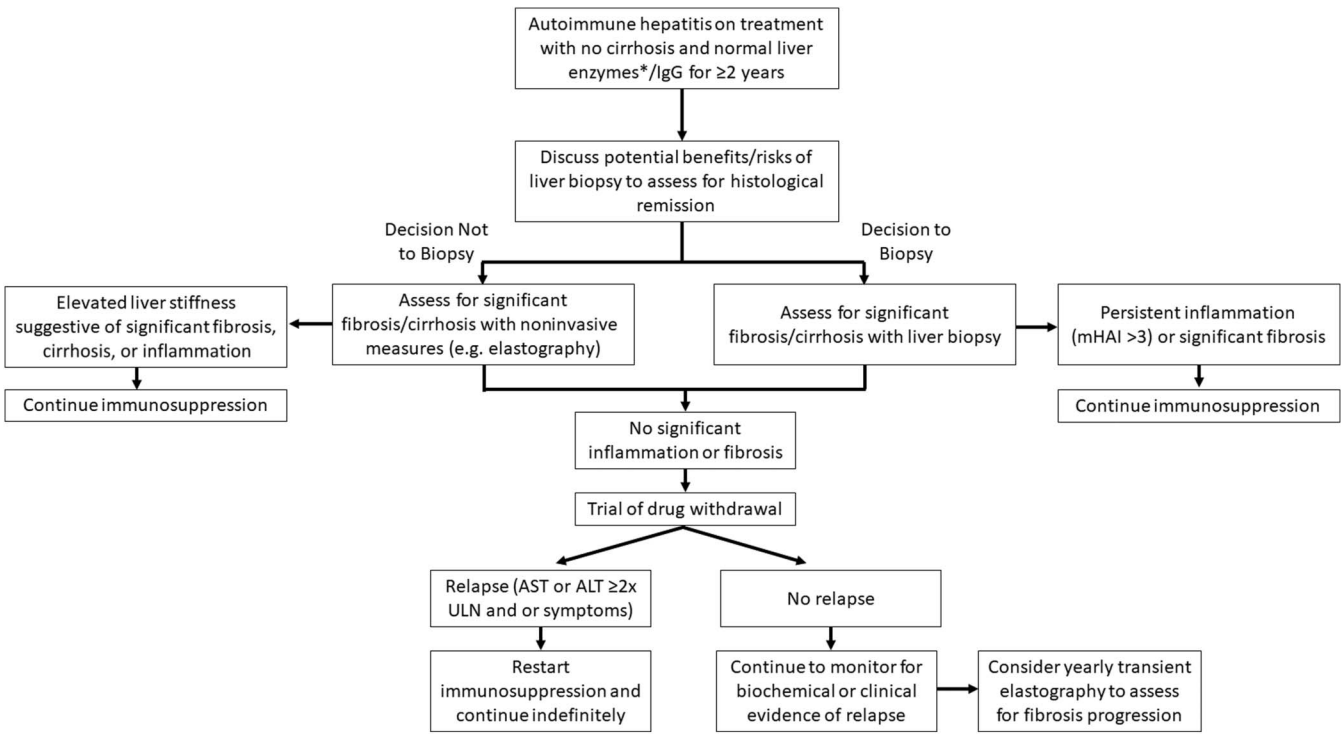

Figure 2. Proposed algorithm for withdrawing drug therapy in AIH. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; mHAI, modified hepatic activity index; ULN, upper limit of normal. Normal ranges for liver enzymes were obtained from the ACG Clinical Guideline for Evaluation of Abnormal Liver Chemistries (17).

remission with immunosuppressive therapy and should be placed on maintenance therapy for a minimum of 2 years except in cases of DIAIH. Long-term therapy beyond this has less certain benefits and may lead to significant treatment-related side effects and medication-related burden. A high proportion of patients with AIH who stop therapy experience a relapse and associated morbidity, but these risks can be minimized with appropriate patient selection and vigilant postwithdrawal monitoring. Future investigation may focus on improving risk stratification tools and developing therapies that alter the underlying immunologic drivers of AIH.

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CONFLICTS OF INTEREST

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