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Review

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The use of immunosuppression in autoimmune hepatitis: A current literature review

Angela Cropley, and Martin Weltman

Department of Gastroenterology and Hepatology, Nepean Hospital, New South Wales, Sydney, Australia

Autoimmune hepatitis (AIH) is an organ specific autoimmune condition which can manifest at any age of life. The heterogeneous nature of this condition means that great variation can be seen in severity, progression of disease and response to treatment within this patient group. Since the 1980s prednisolone and azathioprine have been used for induction and remission of the disease and remain the mainstay of treatment. Other immunosuppressive agents have been employed in difficult to treat cases. While there is less published data regarding these agents compared with the conventional treatments of steroid and azathioprine, there is mounting evidence to support the use of mycophenolate mofetil as a second-line agent. The calcineurin inhibitors, though less studied, additionally show promise. More data is needed on the use of biological agents in refractory disease. This review focuses on our centre's approach to treatment of AIH in the context of a contemporary review of the literature. **(Clin Mol Hepatol 2017;23:22-26)**

Keywords: Autoimmune hepatitis; Immunosuppression; Prednisone; Azathioprine; Mycophenolate mofetil

INTRODUCTION

Autoimmune hepatitis (AIH) is an uncommon though serious and potentially life-threatening disease which requires prompt recognition and treatment by experienced hepatologists. In cases unresponsive to conventional treatment, achieving disease remission can be difficult and institutions may vary in their experience and management of this challenging patient group. The object of this review is to impart our experience in the use of immunosuppression in AIH as well as provide a global perspective in the form of a current literature review.

Autoimmune hepatitis is an organ specific autoimmune disease that manifests as a chronic inflammatory disease of the liver, typically characterized by periportal inflammation, elevated autoantibodies and hypergammaglobulinemia. A variety of clinical presentations can be observed ranging from mild, almost subclinical disease to fulminant hepatitis.[1] While the pathogenesis is not fully understood, the current hypothesis is that an environmental agent is thought to trigger a dysregulated T-cell response against auto antigens in genetically susceptible individuals. A relative paucity of regulatory T-cells amongst an inflammatory milieu driven by effector T-cells sustains and potentiates the disease.[2,3] The worldwide prevalence varies and is 10-20:100,000 in Europe, as high as 43:100,000 in Alaskan populations and as low as 4-5:100,000 in Singapore and Brunei.[4,5] There is a female predominance of 3:1.[6]

Up to a third of patients present with established cirrhosis.[6] A further third present with acute icteric hepatitis, though the majority of patients have subacute disease.[6] Younger patients may

Abbreviations:
AIH, autoimmune hepatitis; MMF, mycophenolate mofetil

Corresponding author : Martin Weltman
Department of Gastroenterology and Hepatology, Nepean Hospital, Derby St, Kingswood New South Wales, Sydney 2747, Australia
Tel: +61-2-4734-2358, Fax: +61-2-47341313
Email: Martin.Weltman@health.nsw.gov.au

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present in a more acute fashion when compared with the elderly.[6] However the prevailing view is that asymptomatic and symptomatic patients should be treated in the same manner, as the disease progression is similar in both groups.[7]

DIAGNOSIS

Clinical practice guidelines are available to aid the accurate diagnosis of AIH. The diagnosis is based on the presence of specific autoantibodies, immunoglobulin levels and histology as well as the absence of acute viral serology.[8,14]

The classical histological hallmark of AIH is interface hepatitis characterised by inflammation and erosion at the junction of the hepatic parenchyma with the portal tracts. Centrilobular lesions and necrosis are present when the disease is severe and progressive. Acute cases may appear histologically indistinct to drug induced liver injury.[9] Fibrosis and cirrhosis may already be evident in subacute disease.[8]

TREATMENT INDICATIONS

Absolute indications for treatment are a serum AST greater than 10 times the upper limit of normal or an AST greater than 5 times the upper limit of normal in conjunction with a serum globulin level greater than 2 times the upper limit of normal. Bridging or multi-lobular necrosis at presentation is an absolute indication for treatment given the risk of progression to cirrhosis.[10] Furthermore, incapavitating systemic symptoms such as fatigue and arthralgia are also considered absolute indications for treatment.[10]

There is less clarity on the outcomes of those patients who present with mild or no symptoms, or mild histological, or laboratory features of disease. As there remains no clear certainty to predict those with a mild disease course, the prevailing view is that treatment is indicated in the vast majority of cases of AIH. Treatment is certainly justified in all patients with evidence of active disease, whether clinical, histological or serological, and especially in those with advanced liver disease.[8,10]

The primary goal of treatment is the complete resolution of symptoms and biochemistry, and the prevention of hepatocellular damage. Furthermore, as AIH is a chronic disorder, the secondary goal is that of prevention of progression of fibrosis leading to cirrhosis.[8]

Corticosteroids, in particular prednisolone (or prednisone), are the key initial therapy and need to be introduced early on in the affected individual. They are effective in 80% of patients with AIH including vulnerable patient subgroup populations such as cirrhotic patients and the elderly.[11-13]

The addition of azathioprine is almost always necessary and often becomes the mainstay of long-term treatment with or without corticosteroids.[8,10,14] However, about 10–20% of patients do not respond adequately to conventional therapy or are intolerant of azathioprine.[11] Failure to respond is characterized by deteriorating liver biochemistry (mainly transaminases) and, in some patients', rapid progression to cirrhosis. Consequently, alternative therapeutic regimens have been used and will be discussed further in this review.

STANDARD TREATMENT

Prednisone

The utility of prednisone in AIH was demonstrated in seminal trials published in the 1970s and 1980s. These studies demonstrated the profound long-term mortality reduction with prednisolone treatment and established its use for induction and remission for AIH.[15,16] However owing to significant side effects with the use of steroids, an alternate agent was sought, particularly for long-term disease control. Subsequent research focusing on azathioprine demonstrated its use as an effective steroid sparing agent for maintenance of disease remission[17,18] and it is the most widely used agent for this purpose today.

Prednisone remains the mainstay of induction therapy and is frequently commenced concurrently with azathioprine on diagnosis. Ideally, upon resolution of liver biochemistry and clinical parameters, azathioprine is continued alone in the remission period. However, this is not always achievable, and frequently prednisone is continued at a low dose to sustain remission. We try where possible to limit long-term prednisone use to 10 mg or less daily in this setting in order to minimise potential steroid adverse effects.

International guidelines recommend induction prednisone of 1 mg/kg/day, up to a maximum of 60 mg/day, when used as the sole agent.[10] This dose is lowered to a maximum of 30 mg/day when used concurrently with azathioprine.[10,14] An alternate approach of administering an induction dose of 60 mg/day of prednisone in conjunction with azathioprine has been demonstrated to achieve more rapid biochemical remission in non-cirrhotic patients.[19] In practice, this more aggressive approach

would be suitable for those patients with more florid acute hepatitis.

Our approach is to commence prednisone concurrently with azathioprine for induction of remission in AIH. In patients with severe acute hepatitis including those patients with fulminant hepatitis intravenous hydrocortisone can be used at 100 mg IV QID. Generally though, we commence oral prednisone 40-50 mg/day in the adult patient. Azathioprine is commenced concurrently at 1 mg/kg/day and is titrated depending on disease response. A suboptimal improvement in clinical parameters and liver biochemistry may prompt further escalation to 2 mg/kg/day to a maximum dose of 200 mg/day. However, patients usually respond to modest doses of 100 mg daily or less.

Commencing azathioprine at diagnosis allows a therapeutic maximum to be reached by the time remission is achieved with steroids and provides time for dosage adjustments prior to the maintenance stage if patient response is indeed suboptimal.

We use 6-mercaptopurine in instances of intolerable gastrointestinal side effects due to azathioprine, as less side effects have been observed with this agent. 6-Mercaptopurine has been employed elsewhere with good effect in AIH.[20]

In contrast to inflammatory bowel disease, measurements of thiopurine metabolites are not a useful guide to therapy in AIH.[21-23] Rather, clinical parameters and transaminase levels guide therapy. In our centre, serial monitoring of mean corpuscular volume, liver function and full blood count is performed to monitor for toxicity.

Oral budesonide is an alternative to prednisone and lessens systemic steroid side effects. It can be given at doses of 3 mg twice or thrice daily in combination with azathioprine.[24] Our experience with budesonide is limited largely secondary to it being a more expensive alternative to prednisone.

There is some evidence that its efficacy does compare favourably with prednisone and patients experience significantly less steroid side effects.[24] On the whole though, there is a paucity of literature in relation to the use of budesonide in AIH particularly its use in patients with refractory disease.

Alternative treatments to Corticosteroids and Azathioprine

In cases of treatment failure with azathioprine or in the case of drug intolerance, we use Mycophenolate mofetil (MMF). It remains the most studied second line agent for the treatment of AIH.[10] It compares favourably with azathioprine as a first line remission agent and is generally well tolerated.[25] It can be given at doses of 1.5 to 2 g daily initially depending on patient tolerance.[10,26]

There is increasing data to suggest that its role is largely in patients who are intolerant to azathioprine, rather than in patients failing conventional treatment.[27,28]

OTHER AGENTS

The Calcineurin inhibitors, cyclosporine and tacrolimus have been used in our centre for the treatment of isolated cases of AIH refractory to conventional therapy with success. Cyclosporin is initiated at 2-5 mg/kg daily and Tacrolimus at 2-6 mg daily. Their common mechanism is ultimate T-cell suppression. As with the more commonly used agents, effectiveness of treatment is monitored by serial measurements of liver biochemistry and the patient's clinical picture. Repeat liver biopsy is generally only required when response to therapy is totally absent or disease progression or a superimposed insult to the liver is suspected.

Cyclosporine has been employed elsewhere in disease refractory to steroids and azathioprine to achieve effective remission.[29,30] However a common pattern observed in the published data to date is the rapid recurrence of disease on dose reduction or cessation of this agent.[8,31,32]

Despite no reports of renal compromise in these studies of cyclosporine in AIH, the potential of renal failure renders it a less attractive agent for long-term remission. Similar renal effects are a potential consequence of tacrolimus use. However, as with cyclosporine, it has been shown to be an effective remission agent in ours and other centres. Its use as a remission agent has been supported by clinical trials.[33,34]

Other immunosuppressants have been less studied and published data are limited to small series and case reports. Our experience is limited with methotrexate and Rituximab. There is a small amount of data to suggest effective remission with the use of these agents elsewhere.[35-37] There are understandably concerns re using methotrexate to treat autoimmune liver disease as it is a known hepatotoxin. Interestingly, use of the biological agent infliximab has been associated with deranged liver function and positive autoantibodies, raising the question as to whether it may precipitate AIH in other clinical contexts.[38] The precise nature of this association has yet to be fully elucidated.[39] Despite this, as a therapeutic agent, it has been shown to be effective in biochemical remission.[40] The immuno-

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suppressants Sirolimus and Everolimus have also been used to achieve partial or complete remission in patients who are refractory to conventional treatment.[41,42] A possible role for their use could be in those unable to tolerate calcineurin inhibitors.

The absolute numbers of patients failing conventional therapy is small, which ultimately limits worldwide expertise in the treatment of this patient group. Our approach in this discrete and challenging group of patients is to use MMF, and then to employ cyclosporine or tacrolimus if MMF is not effective. Regular clinical review and monitoring of renal function is imperative. In our experience patients who remain refractory or have severe fulminant hepatitis to treatment are best referred to a transplant centre. If the disease remains non-fulminant then a biologic agent can be employed and rituximab has been safely employed and is the most studied biologic agent to date in AIH. However, there is no real substantial data on the outcomes when using this agent.

CONCLUSION

Autoimmune hepatitis is an organ specific disease that demonstrates heterogeneity in clinical presentation and disease trajectory. Clinical course is dependent on individual responses to current therapy. While the conventional treatment with steroids and azathioprine is effective in the vast majority of cases, a small proportion of cases fail or do not tolerate standard therapy. To date, the alternative regimes for AIH in this small patient group understandably lack solid prospective data. However MMF is a promising agent and evidence for its efficacy is mounting. We feel it is the most suitable second line agent in refractory disease. Cyclosporin and tacrolimus are also reasonable alternatives. More data is needed into biological therapy before recommending these agents for difficult to treat disease except for salvage therapy.

Conflicts of Interest

The authors have no conflicts to disclose.

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