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Concise Review

The medical treatment for autoimmune hepatitis through corticosteroid to new immunosuppressive agents: A concise review

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Abstract

The treatment of autoimmune hepatitis is evolving as the natural history of the disease and newer agents become available. This concise review will outline the various treatment options in these patients. Treatment with current corticosteroids and azathioprine works in most patients but issues of intolerance and incomplete response arise. These situations led to the investigation of newer immunosupressants including mycophenolate mofetil, budesonide cyclosporine, tacrolimus and ursodeoxycholic acid. The newer agents have been studied in small patient numbers so they are not first-line treatment yet but do have a clear role in those patients with intolerance of incomplete response to standard corticosteroids and azathioprine.

Key words: Remission, ursodeoxycholic acid, azathioprine, mycophenolate mofetil.

Autoimmune hepatitis is a rare chronic inflammatory condition of the liver characterized by circulating specific autoantibodies, elevated transaminases, female predominance and elevated gamma globulin levels.[1] The exact pathogenesis is unknown but thought to be related to aberrant autoreactivity to hepatocytes in patients who are genetically susceptible. In untreated patients with markedly elevated aminotransferase levels more than 5-fold, mortality rates can be up to 80%.[2,3] Once treatment is initiated, a profound improvement is seen with immunosuppressant therapy. There are limitations to current standard therapy including drug toxicity, treatment failure, incomplete response, concomitant obesity, or diabetes mellitus which have lead to the investigation of newer agents for the treatment of autoimmune hepatitis.

Initiation of treatment

Selecting patients for treatment has been well studied. Treatment should be considered once the diagnosis is made using the diagnostic criteria published by the International Autoimmune Hepatitis Group[2] based on both biochemical and histological parameters. These studies have identified patients who are at risk of dying or rapid progression to cirrhosis. Patients with severe activity including an AST greater than 10 times normal, or greater than five times normal with gamma globulin levels two times normal with bridging necrosis or multiacinar collapse benefit most from treatment.[3,4] Some of these patients may present in a acute fulminant manner with marked derangement in the synthetic function of the liver with prolongation of the prothrombin time. Those patients with active cirrhosis, compensated or decompensated, also need treatment but drug toxicities occur more commonly. Patients with moderate activity as defined as modestly elevated AST less than 10 time normal or less than 5 times normal with gamma globulin levels less than 5 times normal or histologic evidence of only interface hepatitis treatment may be considered based on symptoms. Mild autoimmune hepatitis may be seen with mild elevations in AST/ALT and a biopsy showing only scattered plasma cells though the lobule with interface hepatitis. At this time it is unclear if the benefits outweigh the risks in the treatment of mild autoimmune hepatitis as described above. Further studies on alternative therapies such as budesonide and ursodeoxycholic acid are needed in this population.

Standard therapy

The most well studied and effective treatment to date is prednisone alone or in combination with azathioprine. Steroids act quickly by interfering with cytokine produc-

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tion and inhibition of T lymphocyte activation. Azathioprine acts more slowly by blocking the maturation of lymphocyte precursors and may take up to 3 months to demonstrate a biochemical effect on immunosuppression. With steroid monotherapy a typical starting dose of 40-60mg daily is usually initiated and tapered slowly over a 1 month period to a maintenance dose of 20 mg daily. The taper can be a decrease in 10mgs every week. The other regimen used is in combination with azathioprine. With this regimen the prednisone dose is started at 30 mgs and tapered 10 to 5 mgs every week until a maintenance dose of 10 mgs is achieved. Azathioprine at 50 mgs is administered with the prednisone.[5]

The decision to use combination therapy is based on the patient's risk factors for developing complications of steroids. Those patients, who are postmenopausal, obese, diabetic, have hypertension or emotional liability are good candidates for combination therapy. Typically the side effects of steroids are usually present in doses greater than 10 mg daily. Side effects of azathioprine occur in less than 10% of patients and include cytopenias, pancreatitis, gastrointestinal intolerance and cholestatic hepatitis. Prior to initiating therapy with azathioprine, thiopurine methyltransferase (TPMT) activity can be measured to identify those patients at higher risk of bone marrow suppression and toxicity on azathioprine that have pre-existing cytopenias. It should be understood, even with the measurement of TPMT genotyping and phenotyping it is difficult to predict which patient will develop toxicity. Some toxicity may occur independent of TPMT activity and may be more common in advanced fibrosis.[6,7]

As mentioned above, there are some patients who present in a severe fulminant manner with grossly elevated aminotransferases and prolongation of prothrombin time. These patients require aggressive care with large doses of pulsed steroids at doses of 0.5-1.0 g daily. With truly fulminant presentation with severe prolongation of prothrombin time and encephalopathy, the usefulness of steroids has been questioned and may lead the patient to septic complications. Many of these patients will require emergent liver transplantation.[8]

Treatment end points

After initiation of therapy patients should be monitored for signs of clinical and biochemical improvement. A large majority of patients treated with steroids have a substantial lowering of their serum aminotransferase, bilirubin and ã-globulin within 2 weeks.[9] The basic treatment endpoints include remission which is defined as resolution of symptoms, normalization of bilirubin and gamma-globulin levels with an associated decrease in aminotransferases to normal or less than twice normal. An important feature of remission is histological improvement to normal to minimal inflammation without interface hepatitis. The histological remission lags 3-6 months behind biochemical remission so therapy should not be stopped until histological remission is achieved. Treatment failure is defined as worsening clinical, biochemical and histological features despite good compliance with prescribed medications. The development of jaundice, ascites, or hepatic encephalopathy indicates treatment failure and need for liver transplant evaluation. An incomplete response can be seen in an approximately 13-20 percent of patients.[3,10] These patient have some improvement in biochemical, clinical and histologic features but don't achieve remission by three years. An option in these patients is to try high dose prednisone, 40-60 mgs until improvement can be seen.

Maintaining remission

At least 80% of patients with autoimmune hepatitis can be placed into remission with prednisone monotherapy or in combination with azathioprine. Once a follow-up biopsy is obtained showing normal to minimal inflammation, the patient can be considered for drug withdrawal or maintenance therapy. The biopsy can be useful in determining who can remain in remission following cessation of drug therapy. Patients with continued interface hepatitis with normal biochemical markers have a very high rate of recurrence and medications should not be stopped. The withdrawal of therapy can be done with a slow prednisone taper of six weeks or more. Azathioprine can also be withdrawn. These patients should be closely monitored for recurrence. Other authors have advocated long term immunosuppression with azathioprine monotherapy. Williams and colleages followed 72 patients for a median of 67 months on higher dose azathioprine (2 mg/kg) to maintain remission.[11] 83% of these patient maintained their remission and this was deemed safe with the only side effect being lymphopenia. Lower doses of azathioprine have also been used successfully to maintain clinical remission for decades without significant problems with safety.[12]

New therapies

The role of newer, evolving therapies is being established as more clinical trails and experience with newer medications come about. The most studied medications include budesonide, mycophenolate mofitil, cyclosporine, tacrolimus and ursodeoxycholic acid. Most of the experience with these medications has been in patients who have had a failure of standard therapy or developed a contraindication to steroids.

We will now summarize some of the clinical studies involving newer agents for the treatment of autoimmune hepatitis. First budesonide, a second generation corticosteroid with high first pass metabolism, was studied in a series of eighteen treatment-naïve patients. The authors

noted clinical and biochemical remission in fifteen of those treated with 3 mg three times daily.[13] Also, after treatment for at least six months, histologic improvement was seen in a majority of patients at 10 months. Manns *et al.* treated 12 patients for 3 months and found budesonide monotherapy to be effective in inducing complete biuochemical remission in seven patients and a partial response in 3 other individuals. [14] A study by Czaja in 2000 did not show the same promise as these other studies. In this group 10 non-treatment naïve patients, a minority achieved biochemical remission and a total of 7 deteriorated.[15] It is unclear with these small patient numbers how effective budesonide is without future larger trials.

The second well-studied newer immunosuppressant is mycophenolate mofetil. There are case series that showed benefit in small groups of patients resistant or intolerant to aziathioprine treated with mycophenolate mofetil.[16] A recent retrospective review of 15 patients non-responsive or intolerant to standard therapy treated with mycophenolate mofetil in combination or monotherapy showed encouraging efficacy data. Their data showed a significant reduction in biochemical markers, ALT, and inflammation and fibrosis scores without significant side effects.[17] In contrast, in another group of patients with refractory disease, mycophenolate mofetil was compared to high dose steroid therapy and was found to be not uniformly effective.[18] There was some improvement in biochemical scores in some patients but less than in the steroid group. Overall, there is possible benefit by using mycophenolate mofitil in those refractory or intolerant to standard therapy but it should not be used as first line therapy until futher studies are completed.

Cyclosporin and tacrolimus have also been studied in small patient populations with mixed success. In one study of tacrolimus, benefit was achieved but was limited by increasing blood urea nitrogen and creatinine levels.[19]

Ursodeoxycholic acid, mainly used in the setting of primary cholestatic disorders like biliary cirrhosis, has been studied in autoimmune hepatitis with limited success. Biochemical improvement has been seen in 2 series of patients with mild histological improvement.[20,21] The setting in which ursodeoxycholic acid may be the most benifital is autoimmune hepatitis whith cholestatic featues or overlap syndromes. Overlap syndromes, autoimmune hepatitis with histologic features of -primary biliary cirrhosis or primary sclerosis cholangitis, can be treated successfully with immunosuppresion and ursodeoxycholic acid. Two small series have looked at this defined population retrospectively showing benefit in the addition of ursodeoxycholic acid.[22,23]

The treatment of autoimmune hepatitis has become more evidence based as more studies have been published but will continue to be limited due to the rarity of the disease. Hopefully multi-center trails with large patient numbers will be started to better define the efficacy of newer treatments. Until then there is good evidence based data for traditional standard therapy with steroids with or without azathioprine.

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