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Autoimmune Hepatitis: Diagnosis and management

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Abstract

Waldenstrom had first described in 1950 a chronic inflammatory liver disease, now termed as autoimmune hepatitis (AIH). AIH is an unresolving inflammation of the liver of unknown cause, characterized by the presence of interface hepatitis, periportal hepatitis, hypergammaglobulinemia, circulating autoantibodies and response to immunosuppressive treatment in majority of the patients. Prednisone alone or at a reduced dose combined with azathioprine is the conventional treatment. Newer therapies with cyclosporine or tacrolimus have been used as salvage therapy in patients with steroid resistance. Lifetime maintenance therapy may be required, especially for patients with type 2 AIH and those who have cirrhosis at presentation. Liver transplantation has been successful in patients who are refractory or intolerant to immunosuppressive therapy and in whom end stage liver disease has developed.

Key words: autoimmune hepatitis, immunosuppressive therapy, cirrhosis, auto-antibodies, portal plasma cells.

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Introduction

Epidemiology and Natural History

AIH is a rare disorder and its annual prevalence is between 0.1 and 1.2 cases/100,000 in Western Europe and North America. AIH accounts for 6% of liver transplantations in US and 2.6% of liver transplantations in Europe. AIH affects females more than males in the ratio of 3:1; all ages and ethnic groups are susceptible (1).

The natural history of AIH is varied and depends on host issues, which are poorly understood. Forty percent of patients with untreated severe disease die within 6 months of diagnosis (2); at least 40% of survivors develop cirrhosis; 54% develop esophageal varices within 2 years after cirrhosis and 20% patients who develop esophageal varices die from hemorrhage(1). Factors identifying patients with early mortality are serum aminotransferase levels more than 10 fold normal or more than 5 fold normal in conjunction with serum ϒ globulin concentration of at least 2 fold normal(2). Immunosuppressive therapy has changed the course of AIH; only a small number of patients develop cirrhosis during therapy and even fibrosis score tend to improve in up to 70% of patients (3). In children, almost 50% have cirrhosis at the time of presentation and only a few are steroid free until they reach adulthood (4). The elderly patients aged = 60 years have a higher frequency of cirrhosis at presentation than adults aged = 30 years (5). These elderly patients may have an indolent progressive disease that is asymptomatic or masked by other concurrent rheumatic conditions. An acute, even fulminant, presentation may reflect de novo disease or a spontaneous exacerbation of a pre-existent chronic process (5). Elderly patients require treatment, which has a favorable outcome.

Pathogenesis

The cause for liver injury in AIH is probably autoimmunity, which implies the existence of misdirected immune response against self(6). The mechanism for this autoreactivity is probably due to molecular mimicry in which foreign antigens that resemble self-antigens activate lymphocytes. The liver cell injuries in AIH are due to cell-mediated immunity, which is directed against genetically predisposed hepatocytes. Abnormal HLA class II present on the surface of hepatocytes facilitates the presentation of normal liver cell membrane constituents to antigen presenting cells. The cells in turn stimulate the clonal expansion of autoantiantigen-sensitized cytotoxic T

lymphocytes, which in turn infiltrate the liver tissue and destroy liver cells. The abnormal HLA expression may be triggered by genetic factors, viral infections such as Ebstein Barr, cytomegalo, hepatitis A, B, C and D viruses, and drugs such as oxyphenistain, minocycline, etc. These viral and pharmacological agents trigger autoantibody response to various cytochrome P450 (CYP) enzymes expressed in liver and kidney(7). The most convincing evidence is related to hepatitis viruses e.g., hepatitis C virus elicits anti-liver kidney and microsomal (LKM)-1 against CYP2D6 in a subset of individuals during long standing chronic infection; hepatitis D virus elicits anti-LKM-3 against UDP glucouronoyl transferase 1A, etc.

Clinical features and Diagnosis

The clinical spectrum of presentation ranges from no symptoms to severe symptoms and even as acute or fulminant liver failure. The symptoms are non-specific of varying severity and include fatigue, malaise, anorexia, nausea, abdominal pain, arthralgia, jaundice and pruritis. Physical examination may be entirely normal or may reveal hepatomegaly, splenomegaly, jaundice and signs of liver failure. AIH may present for the first time during pregnancy or in the early post partum period.

The diagnosis of AIH is based on various clinical and biochemical findings along with circulating autoantibodies, raised immunoglobulin levels and characteristic histological picture (Table 1) (8). Interface hepatitis and portal plasma cells are the characteristic histological hallmarks of AIH.

Classification of AIH

AIH has been further classified into three types on the basis of presence of autoantibodies (Table 2). These autoantibodies in AIH can exhibit mutual exclusivity, and they have been the basis for designating two types of AIH. They however do not have distinctive etiologies or responses to corticosteroid therapy. International Autoimmune Hepatitis Group (IAHG) has not endorsed them as valid clinical entities but the designations have been useful as clinical and research descriptors.

Type 1 AIH is the most common form of the disease worldwide and is associated with ANA and/or SMA (9). It constitutes 80% of all the cases of AIH. In 48% of cases, AIH type 1 is associated with extrahepatic autoimmune syndromes. It has a strong

Table 1 : Diagnostic criteria (8)

Requisites	**Definite**	**Probable**
No viral infection	No markers of hepatitis A, B, and C viruses	No markers of hepatitis A, B, and C viruses
No alcohol injury	Daily alcohol <25 g/d	Daily alcohol <50 g/d
No toxic injury	No recent use of hepatotoxic drugs	No recent use of hepatotoxic drugs
No genetic liver disease	Normal á1 anti-trypsin phenotype, normal ceruloplasmin, Cu, Fe ferritin levels	Partial á1 antitrypsin deficiency, nonspecific ceruloplasmin, Cu, Fe, ferritin abnormalities
Laboratory features	↑↑ serum ALT/AST, Globulin, ã-globulin or immunoglobulin G level ≥ 1.5x normal	↑↑ serum ALT/AST, Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM-1 ≥ 1:80 in adults and ≥ 1:20 in children; no AMA	ANA, SMA, or anti-LKM-1 ≥ 1:40 in adults or other autoantibodies
Histologic findings	Interface hepatitis, No biliary lesions, granulomas	Interface hepatitis, No biliary lesions, granulomas

Abbreviation: AMA, antimitochondrial antibodies; ANA, antinuclear antibody; AST, aspartate aminotranferase; ALT alanine aminotranferase; anti-LKM, anti-liver kidney and microsomal; SMA, smooth muscle antibody.

Based on recommendations of the International Autoimmune Hepatitis Group (J Hepatol 1999;31:929-938) (8).

association with HLA DR3 and HLA DR4 haplotype. Type 1 AIH has a mild but acute onset and about 25% of patients can have cirrhosis as the initial presentation. It has high titers of ANA and/or SMA. ANA is the most common antibody in AIH. These antibodies do not correlate with disease activity,

progression, and requirement of treatment. SMA frequently occurs in association with ANA. In pediatric population it may be the only autoantibody in cases of AIH and that too in low titer (1:20).

Type 2 AIH is characterized by anti-LKM 1 positivity and the absence of ANA and SMA (9). It is generally considered to have a poor prognosis, but recent reports do not corroborate this premise. Both type 1 and type 2 AIH respond well to corticosteroids.

The existence of type 3 AIH is the most controversial one and is not recognized by IAHG and is the least common of the three subtypes. It is characterized by presence of anti SLA/LP in serum. The clinical and laboratory features are undistinguishable from type 1 AIH and these cases also respond well to immunosuppressive therapy.

Our own experience at Chandigarh (10) and experience from Lucknow (11) confirms the global distribution of AIH by indicating its occurrence in India. The disease, albeit uncommon among chronic liver disorders in India (frequency, ~2%), is similar to that

Table 2 : Classification of AIH

Variable	Type 1	Type 2
Characteristic autoantibodies	ANA , SMA	Anti-LKM1
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Pediatric 2-14 years; rare in adults
Gender	75% women	90% women
Clinical severity	Wide range	Generally severe
Histopathologic features at presentation	Wide range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long term maintenance therapy	Variable	Approximately 100%

found in North America and Northern Europe. Indian patients did not have antibodies to LKM1. Among 54 adult patients [42 women, mean age 43.5 years(range 30-70)] with autoimmune liver disease studied over a period of 10 years (1994 to 2003) 31 had AIH (all type 1 AIH), 13 had primary biliary cirrhosis (PBC) 5 had AIH + PBC overlap, and 5 had AIH + primary sclerosing cholangitis (PSC) overlap. None of the patients with AIH showed presence of anti-LKM 1. The clinical presentations of patients with AIH included jaundice in 17, generalized weakness in 11, pruritus in 9, dryness of eyes in 3. Of the 19 patients with AIH in whom treatment was given only 14 patients achieved remission. Only one of the five patients with AIH + PBC overlap improved on prednisolone, azathioprine and ursodeoxycholic acid. Two patients with AIH+PSC showed partial response to prednisolone, azathioprine and UDCA.

Treatment

AIH is generally responsive to steroid therapy. It was the first chronic liver disease in which the medical treatment was shown to prolong the survival. Three landmark studies in 1970s have shown that prednisone, prednisolone, or prednisone and azathioprine combination therapy but not azathioprine monotherapy have reduced mortality and morbidity in patents with AIH (12-14). These trials have also shown improvement in clinical as well as histological features. The 20-year life expectancy of all treated patients with severe disease exceeds 80% and survival is similar in age and sex- matched patients from same geographical region (15). Corticosteroid therapy also reduces hepatic fibrosis. Fibrosis scores improved in 56% of patients followed for 55 ± 9 months and did not progress in 33% of patients followed for 62 ± 14 months (3). Histological activity indices decreased concurrently, and patients in whom histological activity indices improved had a higher frequency of improvement in fibrosis scores (80% vs 25%, respectively; $p = 0.002$) (3). These findings suggest that improvement in hepatic fibrosis occurs in conjunction with reductions in liver inflammation and that corticosteroid therapy facilitates the disappearance of fibrosis by suppressing inflammatory activity. Patients with histological features of cirrhosis respond well to steroid treatment as do patients without cirrhosis.

Therapeutic trials have not been done in patients with mild disease and the indications for treatment remain uncertain and have to be individualized. The symptoms, disease behavior and potential for drug related

side effects must be balanced against each other. Clinical judgment remains the basis of treatment. Patients with poor outcome are those with advanced inactive cirrhosis, post menopause, osteopenia or vertebral compression, emotional liability or psychosis, poorly controlled hypertension and brittle diabetes.

Indications of treatment

The clear indications of treatment are – relentless progressive disease with disabling symptoms, fulminant presentation, more than ten fold elevation of aminotransferase, patients with aminotransferase levels that are five fold the upper limit of normal in conjunction with a serum ϒ globulin levels at least twice the upper limit of normal and last but not the least is histological features, such as, bridging necrosis or multiacinar necrosis (Table 3) (16). The indications of treatment in children are similar to those in adults. The disease is more severe in children

Table 3 : Indications for treatment

Parameters	Absolute	Relative	No indication
Clinical	Disabling symptoms Relentless clinical progression Fulminant presentation	Mild symptoms	Asymptomatic
Laboratory	Serum AST ≥ 10-fold upper limit of normal Serum AST ≥ 5-fold upper limit of normal and gamma-globulin level ≥ twice normal	Serum AST level 3 to 9 times normal values Serum AST ≥ 5-fold upper limit of normal and gamma-globulin level < twice normal	Serum AST level < 3 times normal values, Severe cytopenia
Histologic	Bridging necrosis or multiacinar necrosis, severe and confluent interface hepatitis	Mild and moderate interface hepatitis	Inactive cirrhosis Focal interface hepatitis Portal hepatitis Decompensated inactive cirrhosis with variceal bleeding or encephalopathy

at the initial presentation probably due to a delay in diagnosis.

Treatment Regimens

There are two treatment regimens which are generally accepted and have similar efficacy. Prednisolone alone or lower dose of prednisolone in conjunction with azathioprine induces clinical laboratory and histological remission with similar frequency (Table 4).

Table 4 : Treatment regimens for adults

	Prednisone only (mg/d)	**Combination**	
		Prednisone (mg/d)	**Azathioprine (mg/d)**
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Maintenance until end point	20	10	50
Reasons for Preference	Cytopenia, thiopurine methytransferase deficiency, pregnancy, malignancy, short course (=6mo)	Postmenopausal state osteoporosis, brittle diabetes, obesity, acne, emotional lability, hypertension	

The combination therapy is associated with lower incidence of side effects than the higher dose of prednisolone regimen (10% versus 44%) and is the preferred treatment (14). Only 13% of patients develop complication to therapy and necessitate dose reduction or discontinuation (14). The common side effects of azathioprine include cholestatic hepatitis, veno-occlusive disease, pancreatitis, nausea, rash and bone marrow depression. These side effects can be minimized by decreasing dose of the drug. Theoretical possibility of malignancy is a long-term complication. The frequency of extrahepatic malignancy is 5% after 42 months of treatment (17). The risk of

malignancy is 14 fold that of age sex matched population (17).

The role of corticosteroids in the treatment of severe acute and fulminant AIH has not been established, but limited experience suggests that the prompt initiation of corticosteroid therapy can be beneficial in 36–100% of such patients (18).

Prednisone alone is given in patients with severe cytopenia, those undergoing short term treatment trial, women who are pregnant or contemplating pregnancy, patients with active malignancy and individuals with thiopurine methyltransferase deficiency (1). Combination therapy is usually recommended for patients who require more than six months of treatment, postmenopausal women, individuals with emotional instability, osteoporosis, brittle diabetics labile hypertension and obesity (1).

Therapy is continued until remission, treatment failure, incomplete response or drug toxicity. There are no predictions for an early or later remission and hence no prescribed minimum or maximum duration of treatment. Remission is indicated by disappearance of symptoms, improvement of serum aminotransferase levels to less than twice normal, restoration of serum bilirubin and γ globulins levels to normal and improvement of the liver tissue to normal, or portal hepatitis or cirrhosis with minimal or no activity (19). Histological improvement lags behind clinical and biochemical improvement by three to six months and treatment should be continued for at least this period. Sixty-five percent of patients enter remission within eighteen months and 80% achieve remission within three years (13).

Appearance of disease activity after remission and termination of therapy indicates relapse. It is characterized by increase in serum aminotransferase levels to more than three times the upper limit and/or increase in serum gamma globulin level to more than 2 g/dL. Patients who relapse have a greater frequency of progression to cirrhosis (40% versus 18%) development of esophageal varices (25% versus 15%) and death from hepatic failure (15% versus 4%) than patients who sustain remission after drug withdrawal (20). Re-treatment with the original regimen typically induces another remission, but relapse recurs in 79% within 6 months after drug withdrawal (21). With each re-treatment and relapse, the frequency of drug-related adverse effects increases and this risk outweighs the low probability of sustained remission with repeated

conventional therapy. Those patients who relapse can be put either on low dose prednisone (22) or on azathioprine to prevent symptoms and maintain serum aminotransferase at low levels.

Treatment failures have been managed with higher dose of prednisone alone (60 mg/day) or prednisone 30 mg/day in conjugation with azathioprine (150 mg/day). The regimen is continued for at least one month and then dose of prednisone is reduced by 10 mg and dose of azathioprine is reduced by 50 mg after each month of clinical and laboratory improvement Dose reduction is continued till maintenance levels of medications are again achieved (1).

Pregnancy

Pregnancy is not a contraindication to treatment. These pregnant females have slightly higher than normal frequency of prematurity, lower birth weight and fetal anomalies. However, concerns continue regarding the use of azathioprine in pregnancy and the behavior of autoimmune hepatitis during this period. Recently reported cases indicate an unpredictable behavior during pregnancy. Fetal mortality of 19% (usually before the twentieth week); perinatal mortality of 4%; and maternal mortality of 3% has recently been reported (23). Hence, prospective collaborative studies are needed to define the consequences of the liver disease and its treatment on the mother and fetus and to formulate universal management strategies.

Emerging treatment strategies

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. These agents promise greater and more site-specific immune suppression than prednisone or azathioprine. These 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. Clinical trials are needed to establish their efficacy, safety and target population.

Cyclosporine has been used as salvage therapy in patients with steroid resistance (24,25). Tacrolimus is an empiric therapy for the refractory patient, and it may allow corticosteroid withdrawal (26). Treatment with

mycophenolate mofetil has shown its benefit in individuals refractory to or intolerant of conventional therapy (27). However, these experiences have been counterbalanced by others who have shown treatment failure or inadequate improvement during administration of this expensive medication (28). Mycophenolate mofetil thus may be useful in corticosteroid-responsive patients who require a nonsteroidal maintenance regimen. Other alternative drugs like ursodeoxycholic acid, budesonide, 6-mercaptopurine, methotrexate, and cyclophosphamide have also been used in various small studies. Larger studies need to be done on these drugs to confirm their role in treatment of AIH.

Liver transplantation is indicated in patients who are refractory or intolerant to immunosuppressive therapy and in whom end stage liver

Table 5 : Alternative immunosuppressive agents in the treatment of autoimmune hepatitis not responding to standard treatment

Drug	**Dose (Therapeutic goal)**	**Side Effects**
Cyclosporine A	5 to 6 mg/kg/BW/ od (induction /maintenance of remission)	Nausea/diarrhea, hypertension, renal insufficiency
Tacrolimus	3-4 mg bd (induction / maintenance of remission)	Nausea/diarrhea, hypertension renal insufficiency pancytopenia
Mycophenolate mofetil	1 g bd (induction / maintenance of remission)	Nausea/diarrhea, leucopenia, CMV- infections
Budesonide	3-mg tid (induction / maintenance of remission)	Rare and resembles those of systemic steroids
Cyclophosphamide	1 to 1.5 mg/kg/BW/ od (induction /maintenance of remission)	Pancytopenia, cystitis
Ursodeoxycholic acid	13–15 mg/kg body weight daily in 2 divided doses (maintenance of remission)	Rare, diarrhea

disease develops. Patient and graft survival after liver transplantation range from 83% to 92%, and the actuarial 10-year survival after liver transplantation is 75% (29). Recurrence is recognized in at least 17% of patients after 5 ± 1 year, especially in individuals receiving inadequate immunosuppression (30).

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