REVIEW ARTICLE

MEDICAL PROGRESS

AUTOIMMUNE HEPATITIS

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AUTOIMMUNE hepatitis is a chronic necroinflammatory liver disorder of unknown cause associated with circulating autoantibodies and a high serum globulin level. Since the first descriptions of the disorder in the 1950s, it has been known by a variety of terms, most commonly "autoimmune chronic active hepatitis," but in 1992 the International Autoimmune Hepatitis Group recommended the term "autoimmune hepatitis" as the most appropriate and least redundant for this disease.[1] It is important to distinguish autoimmune hepatitis from other forms of liver disease because a high percentage of cases respond to antiinflammatory and immunosuppressive treatment. Early diagnosis with appropriate management can prolong survival, improve the quality of life, and defer liver transplantation.[2]

The distinction between autoimmune hepatitis and the other autoimmune liver diseases — namely, primary biliary cirrhosis[3,4] and primary sclerosing cholangitis[5] — is in general based on characteristic clinical, histologic, and immunologic features. Overlap may occur, however, obscuring the classic boundaries between these diseases. Similarly, the presence of hyperglobulinemia or autoantibodies (or both) in chronic viral hepatitis,[6-8] in which the clinical and histopathological features may be identical to those in autoimmune hepatitis, can occasionally blur the distinction between autoimmune and chronic viral hepatitis.

PATHOLOGICAL FEATURES

The histopathological appearance of the liver-biopsy specimen is crucial in determining the diagnosis and severity of the disease. Histologically, autoimmune hepatitis is characterized by a portal mononuclear-cell infiltrate that invades the sharply demarcated hepatocyte boundary (limiting plate) surrounding the portal triad and permeates the surrounding lobule (periportal infiltrate) and beyond (Fig. 1).[9] On occasion it includes a dense plasma-cell infiltrate (Fig. 1C), which led in the past to the use of the term "plasma-cell hepatitis." The periportal lesion, sometimes referred to as piecemeal necrosis, essentially spares the biliary tree but may involve more of the lobule. In all but the mildest forms of autoimmune hepatitis, fibrosis is present, and with advancing disease, especially in the absence of effective therapy, the fibrosis connects portal and central areas ("bridging") and, by distorting the hepatic lobule, ultimately results in cirrhosis. In patients who have a spontaneous or pharmacologically induced remission, the histologic findings may revert to inflammation confined to the portal areas or, if cirrhosis has already ensued, to inactive cirrhosis.

Although the histologic appearance of autoimmune hepatitis is characteristic, it is not specific to the disease. Many of the features seen in autoimmune hepatitis are common to chronic viral hepatitis, drug-associated chronic hepatitis, and a variety of other disorders (Table 1). Primary biliary cirrhosis and primary sclerosing cholangitis may at times be indistinguishable from autoimmune hepatitis but commonly are characterized by a paucity of, inflammation of, or damage to bile ducts (or all three features).[5,9] Since the histologic appearance of primary sclerosing cholangitis may be identical to that of autoimmune hepatitis, cholangiography may be required to make the diagnosis. Fulminant Wilson's disease is difficult to distinguish from severe autoimmune hepatitis. The severity of the histologic lesion may not parallel the severity of the disease noted clinically, but it appears to be the most important prognosticator in chronic hepatitis.[10]

There are two conditions in which features of both autoimmune hepatitis and primary biliary cirrhosis occur. In the so-called overlap syndrome,[11] the histologic findings of autoimmune hepatitis are accompanied by serologic findings of primary biliary cirrhosis, characterized by the presence of antimitochondrial antibodies (directed toward enzymes in the 2-oxo-acid dehydrogenase family). In autoimmune cholangiopathy (also called autoimmune cholangitis and immune cholangiopathy), the histologic features of both autoimmune hepatitis and primary biliary cirrhosis may be present.[12,13]

PATHOGENESIS

A conceptual framework for the pathogenesis of autoimmune hepatitis is that a genetically predisposed host is exposed to an environmental agent, which triggers an autoimmune process directed at liver antigens, causing a progressive necroinflammatory process that results in fibrosis and cirrhosis. The search for the genetic predisposing factor or factors has in large part been directed at the major histocompatibility complex on chromosome 6.[14-17] As in other autoimmune diseases, there are primary associations with the HLA class I B8 and class II DR3 and DR52a loci. There is also a secondary association with HLA-DR4 in white patients and a primary association with HLA-DR4 in Asians. With the use of more sophisticated molecular techniques, genotyping has confirmed the disease association with specific loci in the HLA-DR region and identified specific amino acid sequences in the light chains of the HLA-DR beta molecules as more specific markers.[18] There is also evidence that loci that encode complement products, immunoglobulins, and T-cell receptors

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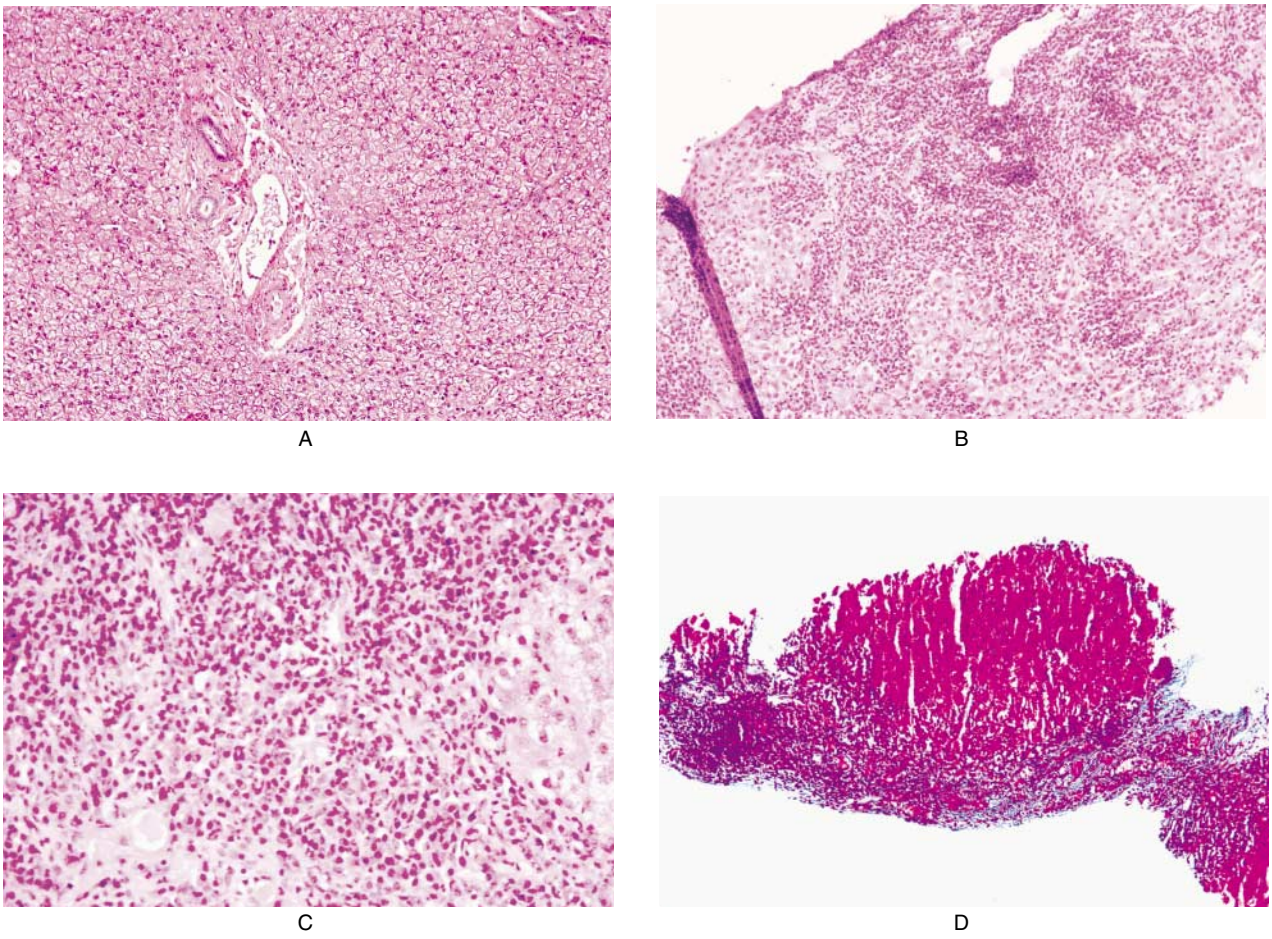

Figure 1. Normal Liver and Liver Affected by Autoimmune Hepatitis.

Panel A shows the portal area and surrounding hepatocytes in a section of normal liver (hematoxylin and eosin, ×100). In Panel B, autoimmune hepatitis is characterized by portal and periportal infiltrates (hematoxylin and eosin, ×100). In Panel C, autoimmune hepatitis is accompanied by a dense plasma-cell infiltrate (hematoxylin and eosin, ×250). Panel D shows autoimmune hepatitis with cirrhosis (trichrome, ×40). A regenerating nodule is visible over a band of fibrosis and inflammation.

play a part in the genetic predisposition to autoimmune hepatitis.[15,19] It has been known for many years that there is an increased prevalence of circulating autoantibodies in first-degree relatives of patients with autoimmune hepatitis. However, studies of families have not provided evidence that this trait has a simple genetic basis or that the presence of autoantibodies is an alternative manifestation of a postulated disease-susceptibility gene conferring a predisposition to autoimmune hepatitis.[20]

The presumed environmental triggering agent or agents important in autoimmune hepatitis are unknown. Autoimmune hepatitis may represent a late sequela of measles infection,[21] and there is some evidence implicating hepatitis viruses and Epstein–Barr virus as initiators of disease.[22-27] It is also possible that interferon treatment of viral hepatitis may activate latent autoimmune hepatitis.[24,25]

Despite extensive investigation into both humoral and cell-mediated aspects of the pathogenesis of autoimmune hepatitis,[28-31] the relevant antigens and the mechanisms underlying the chronicity of necrosis and inflammation remain largely undefined. The circulating antinuclear, anti–smooth-muscle, and antiactin antibodies commonly found in this disease are not organ-specific and do not appear to have a role in pathogenesis, probably serving only as markers of disease. When present in high titers, however, they are more suggestive of autoimmune hepatitis than of other forms of chronic liver disease, in which low titers are occasionally present (see below).

If autoimmune hepatitis represents a disease in which an appropriate immune response occurs to an autoantigen, the asialoglycoprotein receptor, a liver-specific membrane protein, may be a relevant target for cellular cytotoxicity.[28-30] This may explain why circulating antibodies against the asialoglycoprotein receptor are frequently found in patients with autoimmune hepatitis.[32] Their presence in other liver diseases may also reflect autoimmune processes that occur in liver disorders of known cause.

Studies of cellular cytotoxicity, cytokines, and immune regulation have generated hypotheses but have not clarified which abnormalities are primary to the disease

process. The concept of defective suppressor-T-cell function as a mechanism in autoimmune hepatitis, whether primary or secondary, based primarily on in vitro observations, is supported by data demonstrating that dysfunction of these cells can be reversed with glucocorticoid treatment.[33]

Clinical Features and Diagnosis

In order to recognize the clinical features of autoimmune hepatitis, it is important to appreciate their heterogeneity. The clinical features cover a spectrum that extends from the absence of symptoms, in which case the disease is discovered when abnormal serum enzyme values are obtained during a screening examination (or when abdominal surgery is performed), to a severe, acute, sometimes even fulminant hepatitis. Somewhere in between are a variety of mild, nonspecific symptoms that present insidiously and more severe symptoms, including jaundice. Occasionally, autoimmune hepatitis is characterized by profound jaundice, an elevated prothrombin time, and serum aminotransferase values that are markedly elevated — in essence a picture identical to that of severe viral hepatitis. It is important to distinguish this presentation of autoimmune hepatitis from that of acute hepatitis C, which is rare. In early stages of hepatitis C, antibodies against hepatitis C may not be present and the diagnosis depends on the identification of hepatitis C virus RNA by the polymerase chain reaction. In addition to hepatitis A, B, and C, acute hepatitis due to other viruses, such as Epstein–Barr virus, cytomegalovirus, herpesviruses, and hepatitis E in regions where it is endemic, must also be considered in the differential diagnosis of the acute presentation of autoimmune hepatitis. In general, the elevations in serum aminotransferase values are more striking than those of bilirubin and alkaline phosphatase, but on occasion, autoimmune hepatitis can present with a cholestatic picture. In those instances, evidence of extrahepatic obstruction must also be ruled out by imaging studies.

In less severe cases, there may be no correlation between the clinical presentation and biopsy findings. A patient with moderate-to-severe symptoms of more than six months' duration may have extensive inflammatory changes without bridging fibrosis or cirrhosis (Fig. 1B and 1C), whereas an asymptomatic patient may have established cirrhosis (Fig. 1D). The majority of patients, however, have cirrhosis at the time of the initial biopsy.

One characteristic laboratory feature of autoimmune hepatitis, although not universally present, is hyperglobulinemia. Marked elevation of serum globulins, in particular gamma globulins, is often present. As noted, this nonspecific response may also be manifested by the presence of circulating antibodies to non–organ-specific cellular constituents (i.e., autoantibodies); their identification has been particularly helpful in diagnosing autoimmune hepatitis.

The circulating autoantibodies commonly present in classic (type 1) autoimmune hepatitis are antinuclear, anti–smooth-muscle, and antiactin antibodies (Table 2).[34] On occasion, antimitochondrial antibodies in association with antinuclear or anti–smooth-muscle antibodies, or both, are found, but the isolated presence of antimitochondrial antibodies almost always signifies primary biliary cirrhosis, except in rare instances in which an overlap syndrome occurs.[11] Tests for antiactin antibody are not performed in most clinical laboratories, although they are more specific than tests for other antibodies in autoimmune hepatitis; however, titers of anti–smooth-muscle antibody of 1:320 or higher commonly reflect the presence of antiactin antibodies.

Table 1. Histologic Differential Diagnosis of Chronic Hepatitis.

Autoimmune liver disease
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Overlap syndrome
Autoimmune cholangiopathy
Chronic viral hepatitis
Chronic hepatitis B
Chronic hepatitis C
Chronic hepatitis delta
Chronic hepatitis due to other viruses
Chronic drug-induced hepatitis
$Alpha_1$-antitrypsin deficiency
Wilson's disease
Cholangiopathy related to the acquired immunodeficiency syndrome
Granulomatous hepatitis
Systemic lupus erythematosus
Graft-versus-host disease
Alcoholic steatohepatitis
Nonalcoholic steatohepatitis

Since the earliest descriptions of classic (type 1) autoimmune hepatitis, it has been recognized that the disease is more common in women than in men. Although the prevalence of the disease in women is not nearly as high as that of primary biliary cirrhosis, girls and young women are frequently afflicted. In the 1980s a second type of autoimmune hepatitis, now referred to as type 2, was described.[35] This form, which occurs most frequently in girls and young women, is characterized by the presence of circulating antibodies against liver–kidney microsome type 1 (anti–LKM-1) and of anti–liver cytosol 1 antibodies, and sometimes only the latter are present (Table 2).[36-38] Anti–LKM-1 antibodies differ from the anti-LKM type 2 antibodies found in ticrynafen-induced hepatitis and the type 3 antibodies found in chronic hepatitis delta.[34,39,40]

In type 1, or classic, autoimmune hepatitis, a number of circulating autoantibodies other than antinuclear, anti–smooth-muscle, and antiactin antibodies have also been found, which has led to the suggestion that a third type of autoimmune hepatitis may exist.[41] It seems more reasonable to conclude that a variety of antibodies may appear in either of the two major forms of the disease (Table 2). Antibodies against soluble liver antigens (cytokeratins 8 and 18)[42] are found in approximately 10 percent of patients with type 1 autoimmune hepatitis.[43,44]

Antibodies against a liver and pancreatic protein, plasma-membrane sulfatide and nuclear-envelope proteins (lamins A and C), and a variety of anticytoskeleton antibodies have also been described in classic autoimmune hepatitis.[34,45-48] The finding of antineutrophil cytoplasmic antibodies[49-51] has led to the speculation that their presence may indicate a different type of chronic hepatitis.[49] For the most part, however, these antibodies are found in patients with detectable levels of antinuclear antibodies and probably reflect positivity for antinuclear antibodies. Circulating antibodies against the liver-specific asialoglycoprotein receptor are found in a large percentage of European, Asian, and North American patients with autoimmune hepatitis.[32]

In the so-called overlap syndrome, the serologic findings are those of primary biliary cirrhosis, which is characterized by antimitochondrial antibodies, but the histologic findings are those of chronic hepatitis.[11] Autoimmune cholangiopathy[12,13] has clinical features suggestive of primary biliary cirrhosis or primary sclerosing cholangitis (pruritus and high serum alkaline phosphatase levels) in the absence of antimitochondrial antibodies. Histologic features include bile-duct changes, which are more characteristic of primary biliary cirrhosis and primary sclerosing cholangitis. Antibodies against carbonic anhydrase have also been reported.[13]

Some patients present with all the features of autoimmune hepatitis but have no circulating antinuclear or anti–smooth-muscle antibodies. In the future, with the increased availability of tests for other autoantibodies, some of these patients may also be more readily identified as having autoimmune hepatitis; at present they are included in a group described as having cryptogenic cirrhosis.[52] A therapeutic response to antiinflammatory therapy may be the only indication that autoimmune hepatitis is the underlying disease in these patients.

The nonspecific antibody response that occurs in patients with autoimmune hepatitis may on occasion create diagnostic uncertainties for clinicians trying to distinguish between autoimmune diseases and chronic viral hepatitis. Antibodies to hepatitis C have been found in patients with classic autoimmune hepatitis,[53] but they probably represent nonspecific responses that disappear during remission. Since methods are now available to identify circulating hepatitis C RNA, this should no longer be a problem. The occurrence of circulating autoantibodies and rheumatoid factor in a small percentage of patients with chronic hepatitis C virus[6-8,54-58] should also no longer be confusing, except in very rare instances in which chronic viral hepatitis and autoimmune hepatitis coexist or autoimmune hepatitis is triggered during the treatment of viral hepatitis.[24-26] The presence of anti-GOR autoantibodies[54] appears to result from molecular mimicry associated with a hepatitis C antigen.

Table 2. Autoantibodies in Autoimmune Hepatitis.

Type	Characteristic Autoantibodies	Autoantibodies Occasionally Present
1 (classic)	Antinuclear	Antimitochondrial
	Anti–smooth muscle	Anti–soluble liver antigen
	Antiactin	Anti–liver–pancreas protein
	Anti–asialoglycoprotein receptor	Antineutrophil cytoplasmic
		Anti–liver cytosol 1*
2 (anti–LKM-1)	Anti–LKM-1	Antinuclear*
	Anti–liver cytosol 1	

*Rare.

Table 3. Disorders Associated with Autoimmune Hepatitis.

Chronic autoimmune thyroiditis
Hyperthyroidism (Graves' disease)
Ulcerative colitis
Hemolytic anemia
Idiopathic thrombocytopenia
Diabetes mellitus
Diabetes insipidus
Celiac disease
Polymyositis
Myasthenia gravis
Pulmonary fibrosis
Pericarditis
Glomerulonephritis
Acute lichenoid pityriasis
Febrile panniculitis
Hypereosinophilic syndrome
Sjögren's syndrome
Mixed connective-tissue disease

One clue to diagnosing autoimmune hepatitis may be the coexistence of other diseases with immune or autoimmune features. In the spectrum of autoimmune disease ranging from organ-specific to non–organ-specific, autoimmune hepatitis falls somewhere in the middle, since it is often confined to the liver but the antibodies are mostly nonspecific.[59] Nevertheless, autoimmune hepatitis, like primary biliary cirrhosis, can be associated with a number of other autoimmune diseases (Table 3). Although primary sclerosing cholangitis is the autoimmune liver disease most often found with nonspecific ulcerative colitis, autoimmune hepatitis and ulcerative colitis may coexist,[60] and the liver disease may antedate the clinical appearance of disease in the colon.

Primary hepatocellular carcinoma is thought to be a natural consequence of the progression from chronic hepatitis to cirrhosis and ultimately to carcinoma, and this hypothesis applies to autoimmune hepatitis,[61-63] although such progression appears to be less frequent than in chronic viral hepatitis. Recent scrutiny of this problem indicates that in some patients with autoimmune hepatitis who have hepatocellular carcinoma, hepatitis C is a complicating condition.[63] The increased frequency of cancer after long-term treatment of autoimmune hepatitis with azathioprine (Imuran) affects many organs.[62,64]

Treatment

Despite its striking heterogeneity and our incomplete understanding of its pathogenesis, autoimmune hepatitis generally is responsive to corticosteroid therapy.[2,33,65,66] This was noted in early controlled trials despite the fact

that most of the patients had advanced disease and the studies were performed in an era that antedated our ability to test for hepatitis B and C. Although glucocorticoid therapy remains the mainstay of therapy, a reduction in the corticosteroid dose can be accomplished by concomitant administration of azathioprine (steroid-sparing therapy). The remission rate induced by initial therapy is approximately 80 percent.[2] In general, the prognosis is inversely correlated with the histologic severity of disease. Although approximately half the patients remain in remission or have only mild disease activity when the drugs are withdrawn after initial treatment, most eventually require long-term maintenance therapy. Patients whose initial biopsy specimens reveal cirrhosis rarely stay in remission when treatment is withdrawn.

In general, a biochemical response, which is marked by a decrease in serum aminotransferase and globulin levels, occurs within one to three months after the initiation of treatment, although remission has been reported in a small percentage of patients only after years of treatment. Treatment with prednisone (20 to 30 mg) (Table 4) can be instituted in all patients with autoimmune hepatitis in which the histologic appearance is that of severe hepatitis, with or without fibrosis or cirrhosis. In patients in whom mild hepatitis is present on biopsy, the decision to treat is often determined by the symptoms. Patients without symptoms and with mild inflammation need not be treated, but their clinical status and liver-biopsy results should be monitored carefully for evidence of disease progression. To avoid the side effects of glucocorticoid treatment in these patients, particularly postmenopausal women, some physicians elect to begin treatment with a combination of prednisone and azathioprine. Others wait until a remission is induced before starting therapy with azathioprine.

In many patients maintenance therapy with low doses of prednisone alone (5 to 15 mg) or in combination with azathioprine (50 to 150 mg) is successful (Table 4). In some patients long-term maintenance therapy with azathioprine alone, at a dose of approximately 2 mg per kilogram of body weight, is adequate.[67,68] The results of alternate-day treatment with a glucocorticoid and pulsed treatment regimens[69] have been disappointing, and daily therapy is recommended. Before treatment with azathioprine either alone or in combination with a glucocorticoid is begun, its long-term side effects, in particular, bone marrow suppression, immunosuppression, and the long-term risk of cancer, must be weighed against those of glucocorticoid therapy.[62,64,68] A recent report from the United Kingdom suggests the risk of cancer with azathioprine therapy is low.[68]

Once treatment is withdrawn, some patients may stay in remission for months to years. These patients may enjoy long periods during which they do not require antiinflammatory therapy, but therapy should be reinstated when the disease becomes active again. Because of the severe side effects of glucocorticoids, partial suppression of the disease may be preferable and can be achieved with the use of low doses rather than conventional doses of prednisone in patients who have multiple relapses.[70] This approach substantially reduces the severity of side effects without apparently increasing mortality rates or the likelihood of cirrhosis, as compared with conventional therapy. This more loosely controlled approach seems particularly appropriate for postmenopausal women, in whom osteoporosis is of great concern, or for diabetic patients, who may have glucose intolerance as a result of glucocorticoid therapy.

There are no firm guidelines for the withdrawal or reduction of medication. Histologic changes may lag behind biochemical changes, and levels of autoantibodies do not appear to parallel disease activity. A quiescent histologic appearance during therapy is not predictive of maintenance of remission after the discontinuation of treatment. Traditionally, the histologic end points of response have been inactivity or mild activity, reflected by the confinement of inflammatory changes to the portal areas. When treatment fails, sustained activity results in the development or worsening of cirrhosis, with eventual complications and death or the need for liver transplantation.

Although treatment failures occur in only approximately 20 percent of patients with autoimmune hepatitis, they are more frequent in those with established cirrhosis, in patients in whom the disease develops at a young age or with a long duration of disease before therapy, and in patients with the HLA-B8 or DR3 phenotype.[2] The HLA-B8 phenotype is common in patients referred for liver transplantation in both the United Kingdom and North America. It may therefore be a marker for both progression and a relative lack of response to treatment, although sex and age may be confounding variables. These HLA phenotypes may also be markers for the recurrence of autoimmune hepatitis after transplantation.[71] The potential usefulness of cyclosporine and tacrolimus before transplantation is not established.[72-75] Preliminary results with other drugs, including thymosin preparations and ursodiol, have been disappointing.

In this era of liver transplantation, patients with autoimmune hepatitis have excellent survival rates.[2,76] The disease may recur after liver transplantation despite intensive immunosuppression, but it may not appear until the level of immunosuppression has been reduced several years after grafting.[71,76-79] Whether T-cell vaccines, blocking peptides, or monoclonal antibodies may be beneficial before or after transplantation depends on

Table 4. Treatment of Autoimmune Hepatitis.

Type of Therapy*	Monotherapy	Combination Therapy
Initial	Prednisone, 20–30 mg	Prednisone, 10–20 mg, and azathioprine, 50–100 mg
Maintenance	Prednisone, 5–15 mg, or azathioprine, 100–200 mg (approximately 2 mg/kg of body weight)	Prednisone, 5–10 mg, and azathioprine, 50–150 mg

*All medications are given orally in the morning as a single dose.

further investigation and perhaps a better understanding of the pathogenesis of autoimmune hepatitis.

REFERENCES

1. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. Hepatology 1993;18:998-1005.
2. Sanchez-Urdazpal LS, Czaja AJ, van Hoek B, Krom RAF, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. Hepatology 1992;15:215-21.
3. Knox TA, Kaplan MM. Primary biliary cirrhosis: clinical presentation and natural history. In: Krawitt EL, Wiesner RH, eds. Autoimmune liver diseases. New York: Raven Press, 1991:167-73.
4. Lacerda MA, Ludwig J, Dickson ER, Jorgensen RA, Lindor KD. Antimitochondrial antibody-negative primary biliary cirrhosis. Am J Gastroenterol 1995;90:247-9.
5. Lee Y-M, Kaplan MM. Primary sclerosing cholangitis. N Engl J Med 1995; 332:924-33.
6. Lunel F, Abuaf N, Frangeul L, et al. Liver/kidney microsome antibody type 1 and hepatitis C virus infection. Hepatology 1992;16:630-6.
7. Clifford BD, Donahue D, Smith L, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology 1995;21:613-9.
8. Reddy KR, Krawitt EL, Homberg J-C, et al. Absence of anti-LKM-1 antibody in hepatitis C viral infection in the United States of America. J Viral Hepatitis 1995;2:175-9.
9. Batts KP, Ludwig J. Histopathology of autoimmune chronic active hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. In: Krawitt EL, Wiesner RH, eds. Autoimmune liver diseases. New York: Raven Press, 1991:75-92.
10. Lashner BA, Jonas RB, Tang H-S, Evans AA, Ozeran SE, Baker AL. Chronic hepatitis: disease factors at diagnosis predictive of mortality. Am J Med 1988;85:609-14.
11. Davis PA, Leung P, Manns M, et al. M4 and M9 antibodies in the overlap syndrome of primary biliary cirrhosis and chronic active hepatitis: epitopes or epiphenomena? Hepatology 1992;16:1128-36.
12. Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 1993;18: 10-5.
13. Gordon SC, Quattrociocchi-Longe TM, Khan BA, et al. Antibodies to carbonic anhydrase in patients with immune cholangiopathies. Gastroenterology 1995;108:1802-9.
14. Mackay IR, Morris PJ. Association of autoimmune active chronic hepatitis with HL-A1,8. Lancet 1972;2:793-5.
15. Krawitt EL, Albertini RJ. Immunogenetics of autoimmune chronic active hepatitis. In: Meyer zum Büschenfelde K-H, Hoofnagle JH, Manns M, eds. Immunology and liver. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1993:240-9.
16. Donaldson PT, Doherty DG, Hayllar KM, McFarlane IG, Johnson PJ, Williams R. Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. Hepatology 1991;13:701-6.
17. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology 1993;105:1502-7.
18. Doherty DG, Donaldson PT, Underhill JA, et al. Allelic sequence variation in the HLA class II genes and proteins in patients with autoimmune hepatitis. Hepatology 1994;19:609-15.
19. Manabe K, Hibberd ML, Donaldson PT, et al. T-cell receptor constant β germline gene polymorphisms and susceptibility to autoimmune hepatitis. Gastroenterology 1994;106:1321-5.
20. Krawitt EL, Kilby AE, Albertini RJ, et al. Immunogenetic studies of autoimmune chronic active hepatitis: HLA, immunoglobulin allotypes and autoantibodies. Hepatology 1987;7:1305-10.
21. Robertson DAF, Zhang SL, Guy EC, Wright R. Persistent measles virus genome in autoimmune chronic active hepatitis. Lancet 1987;2:9-11.
22. Vento S, Garofano T, Di Perri G, Dolci L, Concia E, Bassetti D. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. Lancet 1991;337:1183-7.
23. Rahaman SM, Chira P, Koff RS. Idiopathic autoimmune chronic hepatitis triggered by hepatitis A. Am J Gastroenterol 1994;89:106-8.
24. Cianciara J, Laskus T. Development of transient autoimmune hepatitis during interferon treatment of chronic hepatitis B. Dig Dis Sci 1995;40:1842-4.
25. García-Buey L, García-Monzón C, Rodriguez S, et al. Latent autoimmune hepatitis triggered during interferon therapy in patients with chronic hepatitis C. Gastroenterology 1995;108:1770-7.
26. Bellary S, Schiano T, Hartman G, Black M. Chronic hepatitis with combined features of autoimmune chronic hepatitis and chronic hepatitis C: favorable response to prednisone and azathioprine. Ann Intern Med 1995; 123:32-4.
27. Vento S, Guella L, Mirandola F, et al. Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. Lancet 1995;346:608-9.
28. Meyer zum Büschenfelde K-H, Lohse AW, Manns M, Poralla T. Autoimmunity and liver disease. Hepatology 1990;12:354-63.
29. Wen L, Peakman M, Lobo-Yeo A, et al. T-cell-directed hepatocyte damage in autoimmune chronic active hepatitis. Lancet 1990;336:1527-30.
30. Löhr H, Treichel U, Poralla T, Manns M, Meyer zum Büschenfelde K-H. Liver-infiltrating T helper cells in autoimmune chronic active hepatitis stimulate the production of autoantibodies against the human asialoglycoprotein receptor *in vitro.* Clin Exp Immunol 1992;88:45-9.
31. Lohse AW, Kögel M, Meyer zum Büschenfelde K-H. Evidence for spontaneous immunosuppression in autoimmune hepatitis. Hepatology 1995;22: 381-8.
32. Treichel U, McFarlane BM, Seki T, et al. Demographics of anti-asialoglycoprotein receptor autoantibodies in autoimmune hepatitis. Gastroenterology 1994;107:799-804.
33. Nouri-Aria KT, Hegarty JE, Alexander GJM, Eddleston ALWF, Williams R. Effect of corticosteroids on suppressor-cell activity in "autoimmune" and viral chronic active hepatitis. N Engl J Med 1982;307:1301-4.
34. Abauf N, Johanet C, Homberg J-C. Autoantibodies in autoimmune chronic active hepatitis. In: Krawitt EL, Wiesner RH, eds. Autoimmune liver diseases. New York: Raven Press, 1991:93-109.
35. Homberg J-C, Abuaf N, Bernard O, et al. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. Hepatology 1987;7:1333-9.
36. Martini E, Abuaf N, Cavalli F, Durand V, Johanet C, Homberg J-C. Antibody to liver cytosol (anti-LC1) in patients with autoimmune chronic active hepatitis type 2. Hepatology 1988;8:1662-6.
37. Abuaf N, Johanet C, Chretien P, et al. Characterization of the liver cytosol antigen type 1 reacting with autoantibodies in chronic active hepatitis. Hepatology 1992;16:892-8.
38. Han S, Tredger M, Gregorio GV, Mieli-Vergani G, Vergani D. Anti-liver cytosolic antigen type 1 (LC1) antibodies in childhood autoimmune liver disease. Hepatology 1995;21:58-62.
39. Duclos-Vallée J-C, Hajoui O, Yamamoto AM, Jacz-Aigrain E, Alvarez F. Conformational epitopes on CYP2D6 are recognized by liver/kidney microsomal antibodies. Gastroenterology 1995;108:470-6.
40. Philipp T, Durazzo M, Trautwein C, et al. Recognition of uridine diphosphate glucuronosyl transferases by LKM-3 antibodies in chronic hepatitis D. Lancet 1994;344:578-81.
41. Manns M, Gerken G, Kyriatsoulis A, Staritz M, Meyer zum Büschenfelde K-H. Characterisation of a new subgroup of autoimmune chronic active hepatitis by autoantibodies against a soluble liver antigen. Lancet 1987;1: 292-4.
42. Wächter B, Kyriatsoulis A, Lohse AW, Gerken G, Meyer zum Büschenfelde K-H, Manns M. Characterisation of liver cytokeratin as a major target antigen of anti-SLA antibodies. J Hepatol 1990;11:232-9.
43. Czaja AJ, Carpenter HA, Manns MP. Antibodies to soluble liver antigen, P450IID6, and mitochondrial complexes in chronic hepatitis. Gastroenterology 1993;105:1522-8.
44. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. Am J Gastroenterol 1995;90:1206-11.
45. Stechemesser E, Klein R, Berg PA. Characterization and clinical relevance of liver-pancreas antibodies in autoimmune hepatitis. Hepatology 1993;18:1-9.
46. Toda G, Ikeda Y, Kashiwagi M, Iwamori M, Oka H. Hepatocyte plasma membrane glycosphingolipid reactive with sera from patients with autoimmune chronic active hepatitis: its identification as sulfatide. Hepatology 1990;12:664-70.
47. Wesierska-Gadek J, Penner E, Hitchman E, Sauermann G. Antibodies to nuclear lamins in autoimmune liver disease. Clin Immunol Immunopathol 1988;49:107-15.
48. Worman HJ, Courvalin J-C. Autoantibodies against nuclear envelope proteins in liver disease. Hepatology 1991;14:1269-79.
49. Hardarson S, Labrecque DR, Mitros FA, Neil GA, Goeken JA. Antineutrophil cytoplasmic antibody in inflammatory bowel and hepatobiliary diseases: high prevalence in ulcerative colitis, primary sclerosing cholangitis, and autoimmune hepatitis. Am J Clin Pathol 1993;99:277-81.
50. Mulder AHL, Horst G, Haagsma EB, Limburg PC, Kleibeuker JH, Kallenberg CGM. Prevalence and characterization of neutrophil cytoplasmic antibodies in autoimmune liver diseases. Hepatology 1993;17:411-7.
51. Targan SR, Landers C, Vidrich A, Czaja AJ. High-titer antineutrophil cytoplasmic antibodies in type-1 autoimmune hepatitis. Gastroenterology 1995; 108:1159-66.
52. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB, Homburger HA. The nature and prognosis of severe cryptogenic chronic active hepatitis. Gastroenterology 1993;104:1755-61.
53. McFarlane IG, Smith HM, Johnson PJ, Bray GP, Vergani D, Williams R. Hepatitis C virus antibodies in chronic active hepatitis: pathogenetic factor or false-positive result? Lancet 1990;335:754-7.
54. Michel G, Ritter A, Gerken G, Meyer zum Büschenfelde K-H, Decker R, Manns MP. Anti-GOR and hepatitis C virus in autoimmune liver diseases. Lancet 1992;339:267-9.
55. Mishiro S, Hoshi Y, Takeda K, et al. Non-A, non-B hepatitis specific antibodies directed at host-derived epitope: implication for an autoimmune process. Lancet 1990;336:1400-3. [Erratum, Lancet 1990;337:252.]

56. Esteban JI, Esteban R, Viladomiu L, et al. Hepatitis C virus antibodies among risk groups in Spain. Lancet 1989;2:294-7.
57. Bianchi FB. Autoimmune hepatitis: the lesson of the discovery of hepatitis C virus. J Hepatol 1993;18:273-5.
58. Zeniya M, Aizawa Y, Watanabe F, et al. HCV-marker-positive autoimmune-type chronic active hepatitis: a possible relation between HCV infection and liver autoreaction. Liver 1994;14:206-12.
59. Roitt IM. Essential immunology. 8th ed. Oxford, England: Blackwell Scientific, 1994:384.
60. Perdigoto R, Carpenter HA, Czaja AJ. Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. J Hepatol 1992;14:325-31.
61. Wang KK, Czaja AJ. Hepatocellular carcinoma in corticosteroid-treated severe autoimmune chronic active hepatitis. Hepatology 1988;8:1679-83.
62. Tage-Jensen U, Schlichting P, Thomsen HF, Høybye G, Thomsen AC. Malignancies following long-term azathioprine treatment in chronic liver disease: a report from the Copenhagen Study Group for Liver Diseases. Liver 1987;7:81-3.
63. Ryder SD, Koskinas J, Rizzi PM, et al. Hepatocellular carcinoma complicating autoimmune hepatitis: role of hepatitis C virus. Hepatology 1995;22:718-22.
64. Wang KK, Czaja AJ, Beaver SJ, Go VLW. Extrahepatic malignancy following long-term immunosuppressive therapy of severe hepatitis B surface antigen-negative chronic active hepatitis. Hepatology 1989;10:39-43.
65. Czaja AJ. Treatment of autoimmune hepatitis. In: Nishioka M, Toda G, Zeniya M, eds. Autoimmune hepatitis. Amsterdam: Elsevier, 1994:283-304.
66. Kuroki T, Monna T, Yamamoto S. Treatment of autoimmune hepatitis in Japan. In: Nishioka M, Toda G, Zeniya M, eds. Autoimmune hepatitis. Amsterdam: Elsevier, 1994:305-16.
67. Stellon AJ, Keating JJ, Johnson PJ, McFarlane IG, Williams R. Maintenance of remission in autoimmune chronic active hepatitis with azathioprine after corticosteroid withdrawal. Hepatology 1988;8:781-4.
68. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995;333:958-63.
69. Czaja AJ, Wang KK, Shiels MT, Katzmann JA. Oral pulse prednisone therapy after relapse of severe autoimmune chronic active hepatitis: a prospective randomized treatment trial evaluating clinical, biochemical, and lymphocyte subset responses. J Hepatol 1993;17:180-6.
70. Czaja AJ. Low-dose corticosteroid therapy after multiple relapses of severe HBsAg-negative chronic active hepatitis. Hepatology 1990;11:1044-9.
71. Devlin J, Donaldson P, Portmann B, Heaton N, Tan K-C, Williams R. Recurrence of autoimmune hepatitis following liver transplantation. Liver Transplant Surg 1995;1:162-5.
72. Mistilis SP, Vickers CR, Darroch MH, McCarthy SW. Cyclosporine, a new treatment for autoimmune chronic active hepatitis. Med J Aust 1985;143:463-5.
73. Hyams JS, Ballow M, Leichtner AM. Cyclosporine treatment of autoimmune chronic active hepatitis. Gastroenterology 1987;93:890-3.
74. Sherman KE, Narkewicz M, Pinto PC. Cyclosporine in the management of corticosteroid-resistant type I autoimmune chronic active hepatitis. J Hepatol 1994;21:1040-7.
75. Van Thiel DH, Wright H, Carroll P, et al. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. Am J Gastroenterol 1995;90:771-6.
76. Ratziu V, Samuel D, Farges O, et al. Liver transplantation (LT) for autoimmune cirrhosis (AIC): evidence of recurrence of primary disease on the engrafted liver. Hepatology 1994;20:Suppl:120A. abstract.
77. Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. Transplantation 1984;37:363-5.
78. Wright HL, Bou-Abboud CF, Hassanein T, et al. Disease recurrence and rejection following liver transplantation for autoimmune chronic active liver disease. Transplantation 1992;53:136-9.
79. Roberts S, Czaja AJ, Charlton MR, et al. Recurrent autoimmune hepatitis following orthotopic liver transplantation. Hepatology 1995;22:Suppl:215A. abstract.