Diagnosis and Treatment of Autoimmune Hepatitis

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Preamble

These guidelines provide a data-supported approach to the diagnosis and management of patients with autoimmune hepatitis. They are based on the following: (1) a formal review and analysis of the published world literature on autoimmune hepatitis (914 articles) (Medline Search from 1966-2002; the search term was autoimmune hepatitis); (2) recommendations developed and published by the International Autoimmune Hepatitis Group; (3) concepts developed at the AASLD Single Topic Conference on autoimmune hepatitis in September 1999; and (4) 40 years of combined experience by both authors in the clinical and laboratory investigation and care for patients with this disease. The guidelines, intended for use by physicians, are meant to be flexible, in contrast to "standards of care," which are inflexible policies to be followed in almost every case. They have been developed in a manner consistent with the American Association for the Study of Liver Diseases' Policy Statement on Development and Use of Practice Guidelines.

Specific recommendations are based on relevant published information. In an attempt to standardize recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases modified the categories of the Infectious Diseases Society of America's Quality Standards. These categories are reported with each recommendation, using the Roman numerals I through IV to determine the quality of evidence upon which the recommendations are based. The categories are as follows: I, evidence from multiple well-designed randomized controlled trials, each involving a number of participants to be of sufficient statistical power; II, evidence from at least one large, well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or from well-designed meta-analysis; III, evidence based on clinical experience, descriptive studies, or reports of expert committees; and IV, not rated.

Background

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause.[1] It is characterized by the presence of interface hepatitis and portal plasma cell infiltration on histologic examination, hypergammaglobulinemia, and autoantibodies.[1,2] Autoimmune hepatitis reflects a complex interaction between triggering factors, autoantigens, genetic predispositions, and immunoregulatory networks.[3,4] The mean annual incidence of AIH among white Northern Europeans is 1.9 per 100,000, and its point prevalence is 16.9 per 100,000.[5] It accounts for 2.6% of the transplantations in Europe[6] and 5.9% in the United States.[7] Women are affected more than men (gender ratio, 3.6:1),[8] and all ages[9,10] and ethnic groups[10-14] are susceptible.

A prospective study has indicated that as many as 40% of patients with untreated severe disease die within 6 months of diagnosis.[15] Cirrhosis develops in at least 40% of survivors[16]; 54% develop esophageal varices within 2 years after cirrhosis[17]; and 20% of individuals with esophageal varices die from hemorrhage.[17] Sustained serum aminotransferase levels of more than 10-fold normal or more than 5-fold normal in conjunction with serum γ-globulin concentrations at least 2-fold normal identify patients with early mortality.[15] Bridging necrosis or multiacinar necrosis on histologic examination progresses to cirrhosis in 82% of patients within 5 years, and mortality is 45%.[18] Patients with less severe laboratory and histologic findings fare better, but cirrhosis still develops in 49% within 15 years and death from hepatic failure occurs in 10%.[19] An acute onset of illness is common (40%),[20-23] and a fulminant presentation, characterized by hepatic encephalopathy within 8 weeks of disease onset, is possible.[24]

Three randomized, controlled treatment trials published between 1971 and 1974 have established that prednisone alone or in combination with azathioprine improves symptoms, laboratory tests, histologic findings, and immediate survival.[15,17,25] Liver transplantation has been associated with 5-year patient and graft survivals that
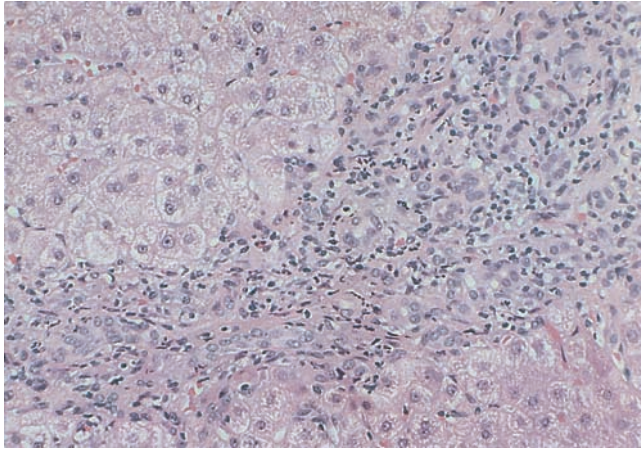
Fig. 1. Interface hepatitis. The portal tract is expanded by a mononuclear infiltrate; the limiting plate is disrupted; and the inflammatory process extends into the acinus. Staining by hematoxylin-eosin; original magnification ×200.

exceed 80%,[26,27] and recurrent disease after transplantation has been usually mild and manageable.[6,28-35] In children, recurrence after transplantation occurs more frequently and may be more difficult to treat.[35]

Diagnostic Criteria

Diagnosis requires the presence of characteristic features and the exclusion of other conditions that resemble AIH.[36,37] Interface hepatitis (Fig. 1) is the histologic hallmark of the syndrome,[2] and portal plasma cell infiltration (Fig. 2) typifies the disorder.[2,36-38] Neither histologic finding is disease specific, and the absence of portal plasma cells does not preclude the diagnosis. All patients suspected of AIH must be evaluated for hereditary (Wilson disease, α_1 antitrypsin deficiency, and genetic hemochromatosis), infectious (hepatitis A, B, and C infection), and drug-induced (minocycline, nitrofurantoin, isoniazid, propylthiouracil, and α-methyldopa) liver injury, some of which may have autoimmune features. The conditions most likely to be confused with AIH are Wilson disease, drug-induced hepatitis, and chronic viral hepatitis, especially chronic hepatitis C.[39-41]

Liver biopsy examination is essential to establish the diagnosis and evaluate disease severity to determine the need for treatment. Serum aminotransferase and γ-globulin levels do not predict the histologic pattern of injury or the presence or absence of cirrhosis.[42] Histologic changes, such as ductopenia or destructive cholangitis, may indicate a variant syndrome of AIH and primary sclerosing cholangitis, AIH and primary biliary cirrhosis, or autoimmune cholangitis,[43-46] and the findings of steatosis or iron overload may suggest alternative diagnoses, such as nonalcoholic fatty liver disease, Wilson disease,

chronic hepatitis C, drug toxicity, or genetic hemochromatosis.[47] Autoantibodies must be present, and the conventional serologic markers of AIH are antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver/kidney microsome type 1 (anti-LKM1).[48,49]

Diagnostic criteria have been codified and updated by an international panel (Table 1).[36,37] Differences between a definite and probable diagnosis of AIH relate mainly to the degree of serum γ-globulin or immunoglobulin G elevation, levels of ANA, SMA, or anti-LKM1, and exposures to alcohol, medications, or infections that could cause liver injury. There is no time requirement to establish chronicity, and cholestatic clinical, laboratory, and histologic changes preclude the diagnosis. The presence of antibodies to asialoglycoprotein receptor (anti-ASGPR), liver-specific cytosol antigen type 1 (anti-LC1), soluble liver antigen/liver pancreas (anti-SLA/LP), actin (anti-actin), and/or perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) support a probable diagnosis if the other conventional markers are absent.

A scoring system has been proposed to assess the strength of the diagnosis (Table 2).[36,37] By weighing each component of the syndrome, discrepant features can be accommodated (normal serum γ-globulin level[50]) and biases associated with isolated inconsistencies (destructive cholangitis[45]) can be avoided. Autoimmune hepatitis typically enters remission during corticosteroid therapy and frequently relapses after drug withdrawal. These characteristic post-treatment responses have also been incorporated into the scoring system. The score based on pretreatment features can be upgraded or downgraded by the response to treatment, and inconsistent findings that
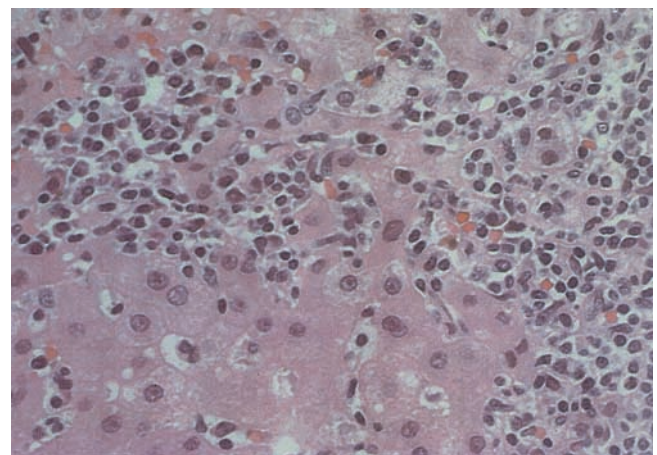

Fig. 2. Plasma cell infiltrate. Plasma cells are identified by their eccentric, clock-face nucleus and pale perinuclear cytoplasmic crescent. They are characteristic of autoimmune hepatitis, but neither pathognomonic of the disease or required for its diagnosis. Staining by hematoxylin-eosin; original magnification ×400.

Table 1. Diagnostic Criteria for Autoimmune Hepatitis

Requisites	Diagnostic Criteria	
	Definite	Probable
No genetic liver disease	Normal α_1 antitrypsin phenotype	Partial α_1 antitrypsin deficiency
	Normal serum ceruloplasmin, iron, and ferritin levels	Nonspecific serum copper, ceruloplasmin, iron, and/or ferritin abnormalities
No active viral infection	No markers of current infection with hepatitis A, B, and C viruses	No markers of current infection with hepatitis A, B, and C viruses
No toxic or alcohol injury	Daily alcohol $<$ 25 g/d and no recent use of hepatotoxic drugs	Daily alcohol $<$ 50 g/d and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality	Predominant serum aminotransferase abnormality
	Globulin, γ-globulin or immunoglobulin G level $\geq$ 1.5 times normal	Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM1 $\geq$ 1:80 in adults and $\geq$1:20 in children; no AMA	ANA, SMA, or anti-LKM1 $\geq$ 1:40 in adults or other autoantibodies*
Histologic findings	Interface hepatitis	Interface hepatitis
	No biliary lesions, granulomas, or prominent changes suggestive of another disease	No biliary lesions, granulomas, or prominent changes suggestive of another disease

Abbreviation: AMA, antimitochondrial antibodies.

*Includes perinuclear anti-neutrophil cytoplasmic antibodies and the not generally available antibodies to soluble liver antigen/liver pancreas, actin, liver cytosol type 1, and asialoglycoprotein receptor.

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

Table 2. Diagnostic Scoring System for Atypical Autoimmune Hepatitis in Adults

Category	Factor	Score	Category	Factor	Score
Gender	Female	+2	Concurrent immune disease	Any nonhepatic disease of an immune nature	+2
Alk Phos:AST (or ALT) ratio	>3	−2	Other autoantibodies*	Anti-SLA/LP, actin, LC1, pANCA	+2
	<1.5	+2			
γ-globulin or IgG	>2.0	+3	Histologic features	Interface hepatitis	+3
(times above upper limit of normal)	1.5-2.0	+2		Plasma cells	+1
	1.0-1.5	+1		Rosettes	+1
	<1.0	0		None of above	−5
				Biliary changes†	−3
				Atypical features‡	−3
ANA, SMA, or anti-LKM1 titers	>1:80	+3	HLA	DR3 or DR4	+1
	1:80	+2			
	1:40	+1			
	<1:40	0			
AMA	Positive	−4	Treatment response	Remission alone	+2
				Remission with relapse	+3
Viral markers of active infection	Positive	−3			
	Negative	+3			
Hepatotoxic drugs	Yes	−4	Pretreatment score		>15
	No	+1	Definite diagnosis		10-15
			Probable diagnosis		
Alcohol	<25 g/d	+2	Posttreatment score		>17
	>60 g/d	−2	Definite diagnosis		12-17
			Probable diagnosis		

Abbreviations: Alk phos, serum alkaline phosphatase level; AST, serum aspartate aminotransferase level; ALT, serum alanine aminotransferase level; IgG, serum immunoglobulin G level; AMA, antimitochondrial antibodies; HLA, human leukocyte antigen.

*Unconventional or generally unavailable antibodies associated with liver disease include perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and antibodies to actin, soluble liver antigen/liver pancreas (anti-SLA/LP), asialoglycoprotein receptor (ASGPR), and liver cytosol type 1 (LC1).

†Includes destructive cholangitis, nondestructive cholangitis, or ductopenia.

‡Includes steatosis, iron overload consistent with genetic hemochromatosis, alcohol-induced hepatitis, viral features (ground-glass hepatocytes), or inclusions (cytomegalovirus, herpes simplex).

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

do not affect treatment response may not alter the diagnosis. The definite diagnosis prior to corticosteroid treatment requires a score greater than 15, whereas the definite diagnosis after corticosteroid treatment requires a score greater than 17 (Table 2).

The original scoring system has been validated against AIH and other chronic liver diseases. The sensitivity of the scoring system for AIH ranges from 97% to 100%,[50-52] and its specificity for excluding AIH in patients with chronic hepatitis C ranges from 66% to 92%.[52-54] In most instances, the scoring system is unnecessary for the diagnosis of AIH since the clinical, laboratory, and histologic components of the syndrome are usually well defined.[50] The major value of the scoring system may be in the objective assessment of variant or atypical syndromes that resemble the classical disease.[43-46,55] Its major weakness has been in excluding cholestatic syndromes with autoimmune features. Among these disorders, the ability of the scoring system to exclude AIH has ranged from 45% to 65%.[50,55] This weakness has justified revision of the scoring system to further downgrade cholestatic findings.[37] Preliminary assessments of the revised system by retrospective analysis of prospectively acquired patient data have indicated a better performance in excluding biliary diseases.[56]

The diagnostic criteria for children are different from those of adults.[36,37] Autoantibody titers tend to be lower in children, and the presence of autoantibodies in any titer, in combination with other requisite elements, is sufficient to support a definite diagnosis (Table 1). Autoantibodies are neither pathogenic nor disease specific,[49] and their expression can vary during the course of AIH.[57] A single low autoantibody titer should never exclude the diagnosis of AIH in an adult or child, nor should high titers establish the diagnosis in the absence of other supportive findings. Seronegative individuals may be classified at presentation as having cryptogenic chronic hepatitis until conventional markers appear later in the course[57-59] or until autoantibodies that are not generally available are tested.[60,61] Autoantibody titers reflect the strength of the immune response, and they are useful only in diagnostic schemes to complement other features that support the diagnosis of AIH. Autoantibodies do not cause the disease nor do their levels reflect response to treatment. Accordingly, they do not need to be monitored.[36,37,41,46]

A unique form of sclerosing cholangitis in children (sometimes termed "autoimmune sclerosing cholangitis") has been described in a single center.[62,63] This disease may mimic classic AIH, and cholangiography is often needed to distinguish the disorders. The small number of reported cases, the lack of general agreement regarding the nature of the process, and the absence of a treatment consequence do not compel the routine performance of cholangiography in the initial evaluation.

Conventional Repertoire of Autoantibodies

ANA, SMA, and anti-LKM1 should be determined in all patients with clinical, laboratory, and/or histologic features that suggest the diagnosis of AIH, and they constitute the conventional repertoire of autoantibodies for this condition.[36,37]

ANA are the traditional markers of AIH, and they are present alone (13%) or with SMA (54%) in 67% of patients with the disease.[57] Nuclear reactivity can be assessed by indirect immunofluorescence on Hep-2 cell lines[64] or by an enzyme immunoassay using microtiter plates with adsorbed recombinant or highly purified antigens.[65] The nuclear targets of ANA in AIH are uncertain, and many ANA in AIH are nonreactive to the major recombinant nuclear antigens.[64] Some medical centers, therefore, prefer to assess ANA by indirect immunofluorescence until the performance parameters of enzyme immunoassay in AIH are fully defined.

ANA in AIH react against diverse recombinant nuclear antigens, including centromere, ribonucleoproteins, and ribonucleoprotein complexes.[64] None of these reactivities has been associated with a specific pattern of indirect immunofluorescence or prognostic importance.[64] Furthermore, the patterns of indirect immunofluorescence (homogenous versus speckled) have had no clinical significance.[66] ANA can be found in primary biliary cirrhosis,[67,68] primary sclerosing cholangitis,[69,70] chronic viral hepatitis,[71,72] drug-related hepatitis,[73,74] nonalcoholic steatohepatitis,[47,75] and alcohol-induced liver disease,[76,77] and their expression can be variable in the same patient.[57]

SMA are directed against actin and nonactin components, including tubulin, vimentin, desmin, and skeletin, and they are also standard markers of AIH.[48,49,78-80] SMA are present in 87% of patients with AIH, either as the sole marker of the disease (33%) or in conjunction with ANA (54%).[57] Three types have been described using cultured fibroblasts treated with vinblastine. These are antibodies to actin, tubulin, and intermediate filaments.[78-80] SMA are present in a variety of liver and nonliver diseases, and their utility as diagnostic markers depends on the clinical syndrome.[69-72,80] Like ANA, SMA have a variable expression in individual patients.[57] Typically, SMA are demonstrated in the clinical laboratory by indirect immunofluorescence on murine stomach and kidney.[49,79-81]

Anti-LKM1 typically occur in the absence of SMA and ANA.[82,83] Seropositivity requires reactivity against the proximal tubules of the murine kidney and the hepato-

cytes of the murine liver by indirect immunofluorescence.[49,83] Antibodies-LKM1 react with high specificity to a short linear sequence of the recombinant antigen, cytochrome mono-oxygenase CYP2D6 (P450 IID6), and they also inhibit CYP2D6 activity *in vitro*.[84,85] These findings together with evidence that liver-infiltrating lymphocytes have specific reactivity to CYP2D6 have implicated this cytochrome as an autoantigen in AIH.[86] Homologies exist between CYP2D6 and the genome of the hepatitis C virus,[84] and occasionally anti-LKM1 can be found in this infection.[87-90] The absence of anti-LKM1 among patients with chronic hepatitis C in the United States[91] may relate to environmental factors, host genetic predispositions, or regional differences in the viral genotype associated with anti-LKM1.[92,93] The anti-LKM1 found in chronic hepatitis C in Europe react to different epitopes on the recombinant CYP2D6 molecule than anti-LKM1 associated with AIH, and these diverse reactivities distinguish the antibodies.[88,94]

Antibodies to LKM1 are rare in the United States, occurring in only 4% of adults with AIH.[83] They have been described mainly in pediatric patients in Europe, but 20% of patients with anti-LKM1 in France and Germany are adults.[82] The reasons for these regional differences in the occurrence of anti-LKM1 in AIH are unknown, but they may reflect variable host expression of CYP2D6, genetic differences in the immune response to the target antigen, or other host-related or region-specific factors.[95,96] The rarity of anti-LKM1 among North American patients does not preclude testing for these markers in patients with suspected AIH who lack other autoantibodies.[36,37,97]

pANCA are common in AIH, and their assay is generally available.[98-100] They have been used to reclassify patients with cryptogenic chronic hepatitis as AIH,[101] but they have not been formally assimilated into the diagnostic algorithm. pANCA do not have diagnostic specificity for AIH nor do they have prognostic implications.[102,103]

Evolving Repertoire of Autoantibodies

New autoantibodies continue to be characterized because they may be imprints of the underlying immunopathic process and clues to an important target autoantigen. Furthermore, they may enhance diagnostic precision and/or be useful as prognostic indices. Antibodies to actin (anti-actin), ASGPR, SLA/LP, and LC1 are in this category. These markers are not generally available, and their assays have not been standardized. They are investigational in nature but of sufficient promise to support the probable diagnosis of AIH.[36,37]

Anti-actin have greater specificity for AIH than SMA.[104] A thermolabile F-actin depolymerizing factor

has been described in serum, and the best assay for detection of anti-actin is unestablished.[105] Preliminary studies using multiple assays have indicated the occurrence of anti-actin in patients who more commonly have HLA DR3, early age onset, and poorer response to corticosteroid therapy than patients without anti-actin.[81] Anti-actin may have a prognostic significance that so far has eluded conventional autoantibodies.[81] They have less sensitivity for AIH than SMA, and they are unlikely to replace SMA as a diagnostic tool.[81]

Anti-ASGPR can coexist with ANA, SMA, and anti-LKM1, and they may also have prognostic importance.[106,107] Anti-ASGPR are directed against a transmembrane glycoprotein on the hepatocyte surface, which can capture, internalize, and display potential antigens.[108] Their presence correlates with histologic activity; their disappearance connotes response to treatment; and their persistence heralds relapse after corticosteroid withdrawal.[109-111] Anti-ASGPR may be generic markers of AIH, biological probes of an important autoantigen, and/or important indices of treatment response.

Anti-SLA/LP are highly specific markers of AIH.[112] A 50-kd cytosolic protein is the target autoantigen,[113] and it is probably a transfer ribonucleoprotein complex (tRNA$^{(Ser)Sec}$) involved in the incorporation of selenocysteine in polypeptide chains[114] or a serine hydroxymethyltransferase involved in the selenocysteine pathway.[115] Anti-SLA/LP do not define a valid subgroup of AIH, but they do allow reclassification of patients with cryptogenic chronic hepatitis as AIH.[60,116] Furthermore, they have been associated with HLA DR3 and a propensity for AIH to relapse after corticosteroid withdrawal.[117] A standardized enzyme immunoassay for anti-SLA/LP has been validated by Western blot using recombinant antigen, and a commercial assay is available in Europe.[112,116] Complementary DNA encodes for the major but not the sole antigenic component of SLA/LP, and the inclusion of a truncated form of the antigen (SLA-p35) within the assay may improve its sensitivity against native SLA/LP.[118]

Anti-LC1 are specific for AIH, and formiminotransferase cyclodeaminase[119,120] and argininosuccinate lyase[121] have been proposed as the antigenic targets. Anti-LC1 are rare in patients older than 40 years, and their prevalence is higher in populations younger than 20 years.[122] Thirty-two percent of individuals with anti-LC1 have anti-LKM1, and in some studies, the antibodies have been associated with concurrent immunologic diseases, marked hepatocellular inflammation, absence of infection with hepatitis C virus, and rapid progression to cirrhosis.[122,123] Recent investigations have contested the clinical importance of anti-LC1 as the antibodies have been absent in children with fulminant AIH, demonstrated in

patients with primary sclerosing cholangitis, and detected in individuals with chronic hepatitis C.[124] Serum levels fluctuate with inflammatory activity in contrast to anti-LKM1, and anti-LC1 may ultimately prove useful as markers of residual hepatocellular inflammation or as probes of an autoantigen associated with disease severity.[125]

Subclassifications

Three types of AIH have been proposed based on differences in their immunoserologic markers.[82,97,126,127] They do not have distinctive etiologies or responses to corticosteroid therapy, and the International Autoimmune Hepatitis Group has not endorsed them as valid clinical entities.[36,37]

Type 1 AIH is the most common form of the disease worldwide, and it is associated with ANA and/or SMA.[97] It affects all age groups, and it is associated with HLA DR3 (*DRB1*0301*) and DR4 (*DRB1*0401*) in Caucasian Northern European and North American patients.[128,129] *DRB1*0301* and *DRB1*0401* influence disease expression and behavior as well as susceptibility. Caucasian patients with type 1 AIH and *DRB1*0301* are younger,[130] and they have a higher frequency of treatment failure,[130] relapse after drug withdrawal,[131] and requirement for liver transplantation[26,27] than patients with other alleles. In contrast, patients with *DRB1*0401* are typically older, frequently have concurrent autoimmune diseases, and respond better to corticosteroids than counterparts with *DRB1*0301*.[130,132] The strong clinical associations with HLA phenotype do not affect the diagnosis and treatment of type 1 AIH, and the class II HLA are not routinely determined.

Type 2 AIH is characterized by anti-LKM1.[82] It is more common in Europe[82,84] and some South American countries[96] than in the United States, and susceptibility may relate to *DRB1*0701*.[95,96] Earlier perceptions that type 2 AIH had a poorer outcome than type 1 AIH[82] have not been corroborated, and both types respond well to corticosteroids.[62] pANCA, which are common in type 1 AIH, are not detectable in type 2 disease.[100]

A distinct form of LKM-positive AIH has been recognized in association with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).[133-135] APECED is due to a single gene defect on chromosome 21q22.3 which may alter thymic deletion of autoreactive T cells.[136-138] It is characterized by ectodermal dystrophy, mucocutaneous candidiasis, multiple endocrine gland failure (parathyroids, adrenals, ovaries), autoantibody production, and AIH in various syndromatic combinations.[133-135] Unlike other autoimmune diseases, APECED has a Mendelian pattern of inheritance, no HLA DR associations, and no female predominance. Patients with the APECED and AIH have a particularly aggressive liver disease that does not respond well to standard immunosuppressive regimens.[133-135]

Type 3 AIH is the least established form of the disease,[97] and it is characterized by the presence of anti-SLA/LP in serum.[126,127] Patients have clinical and laboratory features that are indistinguishable from patients with type 1 AIH, and they respond well to corticosteroids.[60,116]

Recommendations

1. The diagnosis of AIH requires determination of the serum aminotransferase and γ-globulin levels; detection of ANA and/or SMA, or in their absence, anti-LKM1; and liver tissue examination (Rating, III).

2. The diagnostic criteria for AIH that are defined in Table 1 should be applied to all patients (Rating, III).

3. If the diagnosis of AIH is not clear, a scoring method should be used as shown in Table 2 (Rating, II).

Treatment Indications

Three randomized, controlled trials have shown improvement in the clinical and histologic features and survival of severe AIH after corticosteroid therapy.[15,17,25] Subsequent studies have indicated that patients with histologic cirrhosis respond as well to corticosteroid treatment as patients without cirrhosis.[139] Furthermore, the 20-year life expectancy for all treated patients exceeds 80%, and survival is similar to that of age- and sex-matched normal subjects from the same geographical region.[139]

Similar treatment trials have not been performed in patients with less severe disease, and their indications for treatment remain uncertain.[140] Laboratory disturbances of a mild-to-moderate degree are associated with cirrhosis in 49% within 15 years and a 10-year survival of 90%.[19] Untreated patients with interface hepatitis have a 17% probability of cirrhosis within 5 years and normal 5-year life expectancy.[18,141] The benefit-risk ratio of therapy in such patients is undefined, and it may be so low that corticosteroids are unjustified. Furthermore, the patients with mild disease included in the early reports may have had chronic hepatitis C infection, which could not be detected by the available assays.[142] Under such circumstances, the frequency of asymptomatic or mild AIH and its natural history may have been misrepresented.

The indications for corticosteroid treatment in patients with mild AIH must be individualized, and the symptoms, disease behavior, and potential for drug-related side effects must be balanced against each other. Clinical judgment is the principal basis for the treatment

decision. Patients likely to have a poor outcome are those at increased risk for drug intolerance, and they include individuals with advanced inactive cirrhosis, postmenopausal osteopenia or vertebral compression, emotional lability or psychosis, poorly controlled hypertension, and brittle diabetes.[143]

Individuals with cirrhosis at presentation have a higher frequency of drug-related complications than those without cirrhosis (25% vs. 8%), presumably because of increased serum levels of unbound prednisolone resulting from prolonged hypoalbuminemia and/or hyperbilirubinemia.[144,145] Similarly, patients with advanced age and/or menopause are at increased risk for osteopenia and vertebral compression.[146,147]

Postmenopausal patients tolerate initial therapy as well as premenopausal counterparts, and their outcomes are similar.[148] Relapse and retreatment, however, are tolerated less well, and the frequency of vertebral compression is higher in the postmenopausal group.[148] Advanced age, postmenopausal status, and the presence of cirrhosis are features associated with an increased risk of drug-related complications. Each feature, however, does not contraindicate the institution of treatment, and in fact, patients with these characteristics enter remission as commonly as others with disease of similar severity.[140,148-150] The risk of side effects compels careful selection of patients for therapy, and the institution of regular follow-up examinations.

Pregnancy or the contemplation of pregnancy does not contraindicate immunosuppressive therapy.[151-153] Expectant mothers typically respond as well to treatment as others, and there have been only theoretical concerns regarding teratogenicity associated with azathioprine treatment.[154] Skeletal anomalies, cleft palate, reduction in thymic size, hydrops fetalis, anemia, and hematopoietic suppression have been described in mice treated experimentally with higher than pharmacologic doses of azathioprine.[154] These laboratory observations have not been reflected in the human experience, but the use of prednisone alone during pregnancy eliminates any concern.

Pregnant women with AIH have a higher than normal frequency of prematurity, low birth weights, and fetal loss.[151,152] These women typically tolerate pregnancy satisfactorily unless their disease is advanced and complicated by ascites and esophageal varices. Under such circumstances, the risk of variceal hemorrhage may be increased.[155] Patients with advanced liver disease and portal hypertension are commonly amenorrheic and/or infertile, and pregnancy is uncommon. Effective contraception should be advised in those rare, actively menstruating women with advanced liver disease.[155]

Table 3. Indications for Treatment

Absolute	Relative
Serum AST ≥ 10-fold upper limit of normal	Symptoms (fatigue, arthralgia, jaundice)
Serum AST ≥ 5-fold upper limit of normal and γ-globulin level ≥ twice normal	Serum AST and/or γ-globulin less than absolute criteria
Bridging necrosis or multiacinar necrosis on histologic examination	Interface hepatitis

Abbreviation: AST, serum aspartate aminotransferase level.

The indications for treatment in children are similar to those in adults. The disease process in children appears to be more severe at presentation than commonly seen in adults, perhaps because of delays in diagnosis.[62,63,156-158] Over 50% of children have cirrhosis at accession, and the milder forms of the disease described in adults are not typically seen in children.[62,63,156-158] The perceived aggressive course in most children and reports that delays in diagnosis and treatment adversely affect the long-term outcome have justified drug therapy at the time of diagnosis.[62,63,156-158] Only those children with advanced cirrhosis without evidence of inflammatory activity are unlikely to benefit.

The indications for treatment are shown in Table 3.

Recommendations

1. Treatment should be instituted in patients with serum aminotransferase levels greater than 10-fold the upper limit of normal (Rating, I).

2. Patients with serum aminotransferase levels that are 5-fold the upper limit of normal in conjunction with a serum γ-globulin level at least twice the upper limit of normal should be treated (Rating, I).

3. Histologic features of bridging necrosis or multiacinar necrosis compel therapy (Rating, I).

4. Patients not satisfying the criteria in recommendations 1 through 3 must be individualized and treatment should be based on clinical judgment. The presence of interface hepatitis without bridging necrosis or multiacinar necrosis on histologic examination does not compel treatment (Rating, III).

5. Treatment may not be indicated in patients with inactive cirrhosis, preexistent comorbid conditions, or drug intolerances (Rating, III).

6. Treatment is warranted in most children at the time of diagnosis (Rating, II).

Treatment Regimens

Two treatment regimens are comparable with each other and superior to nonsteroidal therapies in the management of severe AIH in adults (Table 4).[143] Prednisone alone or a lower dose of prednisone in conjunction with

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	Postmenopausal state	
	Thiopurine methyltransferase deficiency	Osteoporosis	
		Brittle diabetes	
		Obesity	
	Pregnancy	Acne	
	Malignancy	Emotional lability	
	Short course (≤6 mo)	Hypertension	

azathioprine induces clinical, laboratory, and histologic remission with similar frequency. The combination regimen is associated with a lower occurrence of corticosteroid-related side effects than the higher dose prednisone regimen (10% vs. 44%), and it is the preferred treatment.[143] Advanced cirrhosis can significantly impair the conversion of prednisone to prednisolone, but this impairment is insufficient to alter treatment response or justify the preferential administration of prednisolone.[159]

Eighty percent of patients develop cosmetic changes, including facial rounding, acne, dorsal hump formation, and/or truncal obesity, after two years of corticosteroid therapy.[143] Severe, potentially debilitating complications, such as osteoporosis, vertebral compression, diabetes, cataracts, hypertension, and psychosis, usually develop only after 18 months of continuous therapy and at doses of prednisone that exceed 10 mg daily.[143] Only 13% of treated patients develop complications during therapy that necessitate dose reduction or premature drug withdrawal. The most common reasons for treatment withdrawal are intolerable cosmetic changes or obesity (47%), osteopenia with vertebral compression (27%), and brittle diabetes (20%).[150]

Complications of azathioprine include cholestatic hepatitis,[160] veno-occlusive disease,[161,162] pancreatitis,[163,164] nausea,[143] emesis,[143] rash,[143] and bone marrow suppression.[165,166] Side effects develop in fewer than 10% of patients receiving 50 mg daily of azathioprine, and they can be improved by reduction of the dose or discontinuation of the drug.[143]

Thiopurine methyltransferase mediates elimination of 6-mercaptopurine, and variations in enzyme activity can affect therapeutic action and drug toxicities.[167] The genes encoding thiopurine methyltransferase are highly polymorphic, and enzyme activity is inducible by azathioprine.[167,168] Low enzyme activity is rare and estimated to involve only 0.3% of the population. Heterozygotes with intermediate activity of thiopurine methyltransferase are more common and constitute 11% of the population.[167] There are no data that establish the role of routine testing for thiopurine methyltransferase in AIH, but recommendations have emerged that dissuade the use of azathioprine in individuals with low enzyme activity and the avoidance of high-dose regimens in those with intermediate levels of activity.[169] Pretreatment testing for thiopurine methyltransferase activity is a reasonable clinical precaution, and it should be considered in all patients, especially those with pretreatment cytopenia.

The long-term complications of immunosuppressive therapy include the theoretical possibility of oncogenicity.[170,171] The frequency of extrahepatic malignancy is 5% in patients with a cumulative treatment duration of 42 months.[172] The incidence of extrahepatic malignancy is 1 per 194 patient-years of surveillance, and the probability of tumor occurrence is 3% after 10 years. The risk of malignancy is 1.4-fold that of an age- and sex-matched normal population (range, 0.6 to 2.9), and no specific cell type predominates.[172]

The risk of primary hepatocellular cancer is related mainly to the presence of cirrhosis.[173,174] It is rare in treated patients who do not have hepatitis B and C viruses.[174,175] In a prospective study based on annual assessments of serum α-fetoprotein level and hepatic ultrasonography, only one patient (0.5%) developed primary hepatic malignancy in 1,732 patient-years of observation, and only one of 88 patients with cirrhosis (1%) developed malignancy during 1,002 patient-years after cirrhosis (mean observation interval after cirrhosis, 10 ± 1 years).[174]

Prednisone is appropriate as the sole medication in individuals with severe cytopenia,[165,166] those undergoing a short treatment trial (duration of therapy, <6 months),[143] individuals who are pregnant or contemplating pregnancy,[151] patients with active malignancy,[170] and individuals with thiopurine methyltransferase deficiency (Table 4).[165,166,169] The combination regimen is appropriate in patients who will be treated continuously for at least 6 months or who are at increased risk for drug-related complications, including postmenopausal women and individuals with emotional instability,[143,147,148] osteoporosis, brittle diabetes, labile hypertension, and/or exogenous obesity (Table 4).[143,146,148] Patients receiving prednisone should undergo eye examinations for cataracts and glaucoma periodically during treatment, and those receiving azathioprine in any dose should be monitored for leukopenia and thrombocytopenia.

Adjunctive therapies should be based on an awareness of possible complications of the medication, and they

Table 5. Treatment Regimens for Children

Initial Regimen	Maintenance Regimen	End Point
Prednisone, 2 mg/kg daily (up to 60 mg/d), for 2 weeks either alone or in combination with azathioprine, 1-2 mg/kg daily	Prednisone taper over 6-8 weeks to 0.1-0.2 mg/kg daily or 5 mg daily Azathioprine at constant dose if added initially Continue daily prednisone dose with or without azathioprine or switch to alternate day prednisone dose adjusted to response with or without azathioprine	Normal liver tests for 1-2 years during treatment No flare during entire interval Liver biopsy examination discloses no inflammation

should be introduced as appropriate to the individual's perceived risk. Such therapies might include a regular exercise program, vitamin D and calcium supplementation, estrogen replacement, and the administration of bisphosphonates.[176-178] Asymptomatic patients on long-term corticosteroid treatment should be monitored for bone disease by annual bone mineral densitometry of the lumbar spine and hip.[146]

Treatment regimens have been less rigorously established in children than in adults and to some extent, they reflect the preferences of individual centers.[62,63,156-158,179] There have been no randomized, controlled treatment trials in children with AIH, but several reports of 17 or more children have documented the efficacy of regimens similar to those used in adults (Table 5).[62,63,156-158,179] Despite the severe disease at presentation, the response to treatment with corticosteroids with or without azathioprine is generally excellent in children. Normalization of liver tests is noted after 6 to 9 months of therapy in 75% to 90%.

Prednisone is the mainstay in virtually all reported regimens for children, and it is usually administered initially in a dose of 2 mg/kg daily (up to 60 mg daily) (Table 5).[62,63,156-158,179] Tapering schedules vary widely. In some centers, a rapid switch to alternate day regimens has been advocated, whereas in other centers, maintenance of a daily schedule is considered essential. Because of the significant deleterious effects of long-term intermediate or high-dose corticosteroid therapy on linear growth, bone development, and physical appearance, early use of azathioprine or 6-mercaptopurine for all children without contraindications is usually recommended.[62,63,156-158,179] Experience with azathioprine alone as maintenance therapy has been limited in children, but the drug appears to hold some promise for those who do not tolerate complete cessation of treatment. Regimens incorporating cyclosporin A as initial treatment for children with AIH do not appear to confer a significant advantage over more traditional therapies, and they should be considered investigational.[180-182]

Recommendations

1. Prednisone in combination with azathioprine or a higher dose of prednisone alone is the appropriate treatment for severe AIH in adults (Rating, I).

2. Prednisone in combination with azathioprine is the preferred initial treatment because of its lower frequency of side effects (Rating, II).

3. All patients treated with prednisone alone or in combination with azathioprine must be monitored for the development of drug-related side effects (Rating, III).

4. Azathioprine or 6-mercaptopurine is preferred as a corticosteroid-sparing agent in children, especially when high doses of prednisone are required for disease control (Rating, III).

Treatment End Points

Conventional therapy in adults is continued until remission, treatment failure, incomplete response, or drug toxicity (Table 6).[15,143] There is no prescribed minimum or maximum duration of treatment. All adult patients should be given the opportunity to enter a sustained remission by discontinuing medication after clinical, laboratory, and histologic resolution.[150,183,184] Therapy should not be instituted with the intention of being indefinite.[184] Ninety percent of adults have improvements in the serum aminotransferase, bilirubin, and γ-globulin levels within 2 weeks.[185] Adults rarely achieve remission in less than 12 months, and the probability of remission during therapy diminishes after 2 years.[15,20,150,183,184,186] Histologic improvement lags behind clinical and laboratory improvement by 3 to 6 months, and treatment should be continued for at least this period.[15,42]

Remission connotes disappearance of symptoms, improvement of serum aminotransferase levels to less than twice normal, restoration of serum bilirubin and γ-globulin levels to normal, and improvement of the liver tissue to normal, portal hepatitis, or cirrhosis with minimal or no activity (Table 6).[15,150,183,184,186] Sixty-five percent of patients enter remission within 18 months, and 80%

Table 6. End Points of Initial Treatment and Courses of Action

Treatment End Point	Criteria	Courses of Action
Remission	Disappearance of symptoms Normal serum bilirubin and γ-globulin levels Serum aminotransferase level normal or less than twice normal Normal hepatic tissue or minimal inflammation and no interface hepatitis	Gradual withdrawal of prednisone over 6-week period Discontinuation of azathioprine Regular monitoring for relapse
Treatment failure	Worsening clinical, laboratory, and histologic features despite compliance with therapy Increase of serum aminotransferase by 67% Development of jaundice, ascites, or hepatic encephalopathy	Prednisone, 60 mg daily, or prednisone, 30 mg daily, and azathioprine, 150 mg daily, for at least one month Reduction of dose each month of improvement until standard maintenance levels
Incomplete response	Some or no improvement in clinical, laboratory, and histologic features during therapy Failure to achieve remission after 3 years No worsening of condition	Reduction in doses of medication to lowest levels possible to prevent worsening Indefinite treatment
Drug toxicity	Development of intolerable cosmetic changes, symptomatic osteopenia, emotional instability, poorly controlled hypertension, brittle diabetes or progressive cytopenia	Reduction in dose or discontinuation of offending drug depending on severity of side effect Maintenance on tolerated drug in adjusted dose

achieve remission within 3 years (mean duration of treatment to remission, 22 months).[15,20,150] Daily maintenance doses of medication should remain fixed in adults until remission is achieved (Table 4). Titrations in dose are associated with delayed or incomplete histologic improvement, and it can prolong the durations of therapy.[143] Alternate day schedules of prednisone can induce symptomatic and laboratory improvement, but nonsteroidal or placebo therapies are as effective in achieving histologic resolution.[143]

Liver biopsy assessment prior to termination of treatment is preferred, but not essential, in the management of patients who satisfy clinical and laboratory criteria for remission.[15,150] Interface hepatitis is found in 55% of patients with normal serum aminotransferase and γ-globulin levels during therapy,[42] and these individuals invariably relapse after cessation of treatment.[150] Their recognition by liver biopsy examination prior to drug withdrawal can extend treatment and limit this consequence.[150]

Relapse connotes recrudescence of disease activity after induction of remission and termination of therapy.[42,186,187] It is characterized by an increase in the serum aminotransferase level to more than 3-fold the upper limit of normal and/or increase in the serum γ-globulin level to more than 2 g/dL.[15,42,183,184,186] Laboratory changes of this degree are invariably associated with the reappearance of interface hepatitis in the liver tissue, and they preclude the need for a liver biopsy examination to document relapse.[42] Patients who relapse have a greater frequency of progression to cirrhosis (40% vs. 18%), development of esophageal varices (25% vs. 15%), and death from hepatic failure (15% vs. 4%) than patients who sustain remission after drug withdrawal.[150,183,184] Only the higher occurrence of drug-related side effects in those who relapse and

require re-treatment, however, distinguishes the groups (54% vs. 26%, $P = .05$).[150,183,184]

Relapse occurs in from 20% to 100% of patients who enter remission, depending in part on the histologic findings prior to drug withdrawal.[150,183,186-188] The ideal histologic end point is reversion to normal liver tissue. Adults achieving this result have a 20% frequency of subsequent relapse.[150] In contrast, patients with portal hepatitis at termination of therapy have a 50% frequency of relapse within 6 months,[150,187] and those who progress to cirrhosis during treatment or who have interface hepatitis at drug withdrawal commonly relapse.[150] Not all patients are able to achieve histologic resolution, and pursuit of this ideal end point must be balanced against the risks associated with the continued administration of medication.[150]

Corticosteroids are withdrawn in a gradual fashion over a 6-week period after induction of remission.[15,183,186] The activity of the disease during and after drug withdrawal is assessed by the appearance of symptoms (fatigue, arthralgias, and anorexia), the nature of the physical findings (jaundice, ascites, and/or peripheral edema), and the behavior of the laboratory indices of liver inflammation (serum aminotransferase and γ-globulin concentrations) and function (serum bilirubin and albumin levels, prothrombin time).[42] Laboratory tests are performed frequently during drug withdrawal and for 3 months after termination of therapy.[183-187] They are then repeated at 3 months and then every 6 months for at least 1 year.

Treatment failure connotes clinical, laboratory, and histologic worsening despite compliance with conventional treatment schedules, and it occurs in at least 9% of patients (Table 6).[15,189] The serum aminotransferase level should increase by at least 67% of the pretreatment value to qualify for this designation.[15,189] The inability to enter

remission with protracted therapy and the development of drug-induced complications do not represent treatment failure.

Treatment failure justifies the discontinuation of conventional treatments, and institution of high-dose therapy with prednisone alone (60 mg daily) or prednisone (30 mg daily) in conjunction with azathioprine (150 mg daily) (Table 6).[15,189] Seventy percent of patients improve their clinical and laboratory findings within 2 years, and survival is preserved.[189] Histologic remission is achieved in only 20%, and most patients remain on therapy and at risk for drug-related side effects and/or disease progression. The development of hepatic encephalopathy, ascites, and/or variceal hemorrhage during therapy for treatment failure is an indication for liver transplantation.[26]

Protracted therapy that has improved the clinical, laboratory, and histologic indices but not induced remission constitutes an incomplete response (Table 6).[190] Thirteen percent of patients experience this outcome. Eighty-seven percent of individuals who enter remission during treatment do so within 3 years. Thereafter, the probability of remission during conventional therapy decreases as the risk of drug-related complications increases.[190] In these instances, alternative strategies must be considered.

Drug toxicity justifies premature discontinuation or alteration of conventional therapy in 13% of patients (Table 6).[15,150] In these instances, therapy with the tolerated agent (prednisone or azathioprine) can frequently be maintained in adjusted dose to control disease activity.

The treatment end points for children are similar to those of adults. Almost all children demonstrate improvement in liver tests within the first 2 to 4 weeks of treatment with either prednisone or prednisone and azathioprine.[62,63,156-158] Eighty to 90% achieve laboratory remission in 6 to 12 months. In most treatment protocols, high-dose prednisone (2 mg/kg daily) is administered for up to 2 weeks, at which time a gradual decrease in dose is undertaken to reach a maintenance level (usually 0.1-0.2 mg/kg daily or 5 mg daily) in 6 to 8 weeks (Table 5). Clinical and laboratory parameters rather than histologic findings determine the adequacy of response on therapy. Flares in disease activity, as assessed by an increase in serum aminotransferase level, are treated with a temporary increase in corticosteroid dose.

The goal of treatment in children is to have minimal or no serum aminotransferase abnormality on the lowest dose of medication possible. Long-term, low-dose therapy is anticipated and emotional, cosmetic, and growth-related side effects temper treatment in an individualized fashion. Routine monitoring of conventional liver tests, blood counts, and amylase is performed at 4- to 6-week intervals. The decision to terminate therapy in children is based on laboratory evidence of prolonged inactivity, and it is a consideration in only 20% to 30% of patients. Drug withdrawal is considered in children who have had normal liver tests and no need for increased corticosteroid dose after 1 to 2 years of treatment. At that time, a liver biopsy examination should be performed and therapy withdrawn only if there is no histologic evidence of inflammation. Relapse after drug withdrawal occurs in 60% to 80% of children, and parents and patients must be informed that the probability of re-treatment is high.[62,63,156-158]

Recommendations

1. Conventional treatment regimens should be continued in adults and children until remission, treatment failure, incomplete response, or drug toxicity. Once disease remission has been achieved, drug withdrawal should be attempted (Rating, II).

2. Treatment in children should be adjusted to clinical and laboratory findings in an individualized fashion, recognizing that therapy is frequently long term (Rating, III).

Management of Relapse After Drug Withdrawal

Two strategies have been used in adult patients who have relapsed at least twice. The indefinite low-dose prednisone strategy employs the lowest dose of medication possible to prevent symptoms and maintain serum aminotransferase levels below 5-fold normal.[191] The prednisone dose is reduced by 2.5 mg each month until the lowest dose is reached below which there is clinical and/or biochemical instability. Serum aminotransferase levels must be checked each month as small decrements in prednisone dose can be associated with marked increases in the serum aminotransferase level.[191,192] This strategy is most appropriate in patients who are taking prednisone as their sole drug. It can also be applied to individuals taking prednisone and azathioprine. In these latter instances, the dose of prednisone is first reduced to the lowest dose to prevent biochemical instability. Azathioprine is then discontinued as the dose of prednisone is readjusted to compensate for the withdrawal.[184,191]

Eighty-seven percent of patients can be managed in this fashion on 10 mg of prednisone daily or less (median dose, 7.5 mg daily). Observation intervals for up to 149 months have indicated satisfactory outcomes that have justified continued application of the strategy. Side effects associated with the earlier conventional treatments improve or disappear in 85% of patients; new side effects do not develop; and survival is unaffected.[191] The major ad-

vantages of the low-dose prednisone schedule are avoidance of long-term azathioprine therapy in fertile young adults and elimination of the theoretical risks of oncogenicity and teratogenicity.

The indefinite azathioprine strategy substitutes azathioprine for prednisone after induction of remission.[193,194] The substitution is intended to maintain quiescence of the liver disease indefinitely and avoid corticosteroid-related complications. Application of this strategy is easiest in patients taking prednisone and azathioprine. The dose of azathioprine is increased to 2 mg/kg daily, and then the dose of prednisone is decreased by 2.5 mg each month until complete withdrawal. Patients taking prednisone only can be switched to the azathioprine schedule by adding azathioprine (2 mg/kg daily) and then reducing the prednisone dose by 2.5 mg each month.

Eighty-seven percent of adult patients managed by the indefinite azathioprine strategy remain in remission during a median observation interval of 67 months.[194] Follow-up liver biopsy assessments show inactive or minimal histologic disease in 94% of instances; corticosteroid-related side effects improve or disappear in most patients; and the drug is generally well tolerated.[194] The most common side effect is withdrawal arthralgia, which is encountered in 63% of patients. Myelosuppression occurs in 7%, lymphopenia in 57%; and diverse malignancies in 8%.[194] The major advantage of the azathioprine regimen is the avoidance of corticosteroids and its possible side effects, especially in the postmenopausal patient.

The long-term prednisone and azathioprine strategies for relapse have not been compared head to head in adults, and there are no objective bases for preference. Recent retrospective analyses have indicated that the long-term maintenance therapies need not be life long.[184] Twelve percent of patients treated with these schedules were able to be permanently withdrawn from medication after 69 ± 8 months of follow-up, and the probability of a sustained remission after total drug withdrawal was 13% after 5 years.[184] These observations justify periodic efforts at drug withdrawal in all patients. Bolus regimens of high-dose prednisone[195] and adjunctive treatments with ursodeoxycholic acid[196] and budesonide[197] have not been useful in adults.

Relapse in children is characterized by any manifestation of recrudescent hepatic inflammation after drug withdrawal. Its frequency in children is the same or higher than that observed in adults.[62,63,156-158,179] The occurrence of relapse in children justifies reinstitution of the original treatment regimen. Indefinite low-dose therapy can then be instituted after suppression of disease activity using prednisone in combination with azathioprine or 6-mercaptopurine.[62,63,156-158,179] The experience with azathioprine alone as maintenance therapy is limited in children, and the drug is not widely used as the sole medication.

Recommendations

1. Relapse is common in adults and children after drug withdrawal, and patients should be monitored for this occurrence by regular determinations of serum aminotransferase, bilirubin, and γ-globulin levels (Rating, II).

2. Adults who have relapsed more than once should be treated with combination prednisone and azathioprine therapy, low dose prednisone, or azathioprine only (Rating, II).

Management of Suboptimal Responses to Initial Therapy

Treatment failure is managed with high doses of prednisone alone (60 mg daily) or prednisone (30 mg daily) in conjunction with azathioprine (150 mg daily) (Table 6).[15,189] The regimen is continued for at least 1 month, and then the dose of prednisone is reduced by 10 mg and the dose of azathioprine is reduced by 50 mg after each month of clinical and laboratory improvement. Dose reduction is continued until conventional maintenance levels of medication are again achieved.[15,189]

Alternative management strategies for treatment failure in adults have included the administration of cyclosporine,[198-203] ursodeoxycholic acid,[196] budesonide,[197] 6-mercaptopurine,[204] methotrexate,[205] cyclophosphamide,[206] and mycophenolate mofetil.[207] In each instance, experiences have been small and anecdotal, and in most reports, the preliminary results have been encouraging. Only ursodeoxycholic acid has been evaluated by randomized controlled clinical trial, and it is the one negative experience.[196]

Liver transplantation is effective in patients who deteriorate during or after corticosteroid treatment.[26-29] The 5-year patient and graft survival after liver transplantation in adults ranges from 83% to 92%[26-29]; the actuarial 10-year survival after transplantation is 75%[29,208]; autoantibodies and hypergammaglobulinemia disappear within 1 year in most patients[26,27]; and disease recurrence is typically mild and easily managed.[27-35] Rarely, recurrent AIH may progress to cirrhosis, cause graft failure, and/or be recalcitrant to conventional immunosuppressive regimens.[28,35,209] In such instances, other agents may be successful in controlling the recurrence as exemplified by a single patient whose recurrent disease progressed during therapy with cyclosporine and corticosteroids but responded after treatment with tacrolimus.[209]

There are no findings prior to therapy that predict immediate and long-term outcome, and all decompensated patients with severe inflammation should be given a treatment trial of corticosteroids before proceeding with transplantation.[185] Some individuals with advanced liver disease, ascites, and/or endogenous encephalopathy at presentation will improve with treatment and immediate liver transplantation can be avoided.

The likelihood of a significant response to corticosteroid treatment can be determined within 2 weeks.[185] Resolution of at least one laboratory abnormality, improvement in the pretreatment hyperbilirubinemia, and/or failure of any test to worsen during the treatment period indicates that therapy will be effective short term.[185] Conversely, the presence of multiacinar necrosis and a hyperbilirubinemia that does not improve after 2 weeks identifies individuals who will not survive without urgent transplantation.[185] Long-term survival and the ultimate need for liver transplantation also depend on the response to corticosteroid therapy. Inability to induce remission after 4 years of continuous treatment identifies a subgroup of adults at risk for liver failure.[26] Liver transplantation should be considered in these individuals at the first sign of decompensation. The development of ascites is the most common indication.[26]

Treatment failure is noted in 5% to 15% of children with AIH.[62,63,156-158,179] Children who deteriorate despite compliance with corticosteroid therapy are managed in the same fashion as adults,[62,63,156-158,179] and liver transplantation is an important treatment option. The frequency of recurrent AIH in the allograft is greater in children than in adults after liver transplantation.[35] Recurrent AIH has not been uniformly responsive to treatment, and it has resulted in graft loss in several patients.[35]

Another confounding factor after transplantation in adults[210,211] and children[212-214] is the development of AIH *de novo* in the graft. This may occur after transplantation for autoimmune[210,211] and nonautoimmune diseases.[212-215] *De novo* AIH occurs in 2.5% to 3.4% of allografts, and children seem to have a predilection for the syndrome.[212-214] Immunosuppression with cyclosporine is commonly associated with its occurrence, and the drug may impair thymic negative selection of autoreactive immunocytes.[212,216] In adults, thymic dysfunction is less likely, but there may be promiscuous lymphocytes that have been primed by repeated exposures to diverse but homologous antigens. These "primed" immunocytes may then target the liver because of molecular mimicry within the liver cells.[216] Most patients with *de novo* disease respond to prednisone alone or in combination with azathioprine, but fibrosis and graft loss can occur, especially if corticosteroid therapy is not instituted.[214,215]

An incomplete response is managed empirically by reducing the dose of prednisone to as low as possible to maintain the serum aminotransferase level below 5-fold normal.[191] Azathioprine can be used as a corticosteroid-sparing agent, and it can be added to the regimen or increased in dose to 2 mg/kg daily as the dose of prednisone is reduced.[193,194] Efforts to decrease the dose of medication or eliminate the drugs should be continued throughout follow-up as some patients may achieve remission.[184]

Drug toxicity compels immediate adjustments in therapy.[15,143] Cytopenia, nausea, emotional lability, hypertension, cosmetic changes, and diabetes are typically dose related. These consequences can improve with dose reduction. Severe reactions, including psychosis, extreme cytopenia, and symptomatic osteopenia with or without vertebral compression, justify immediate discontinuation of the offending agent. In these patients, treatment can usually be continued with the single tolerated drug (prednisone or azathioprine) in adjusted dose (Table 6).

Cyclosporine,[202,203] 6-mercaptopurine,[204] cyclophosphamide,[206] and mycophenolate mofetil[207] have also been used successfully after drug toxicity in isolated cases. In children, concerns about the immediate and long-term consequences of prednisone and azathioprine therapy have generated an enlarging clinical experience with cyclosporine, either as primary or salvage therapy.[180-182] All experiences have been preliminary or anecdotal in nature, and the incorporation of cyclosporine into a standard management algorithm has not been justified.

Recommendations

1. High doses of prednisone alone or prednisone in combination with azathioprine should be used in treatment failure (Rating, III).

2. Corticosteroid therapy should be considered in the decompensated patient (Rating III).

3. Liver transplantation should be considered in the decompensated patient who is unable to undergo or be salvaged by drug therapy (Rating, III).

4. Children who have treatment failure should be treated with high-dose corticosteroid regimens and considered for liver transplantation (Rating, III).

Appendix

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