

## Diagnosis and Management of Autoimmune Hepatitis: Current Status and Future Directions

Albert J. Czaja

*Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA*

Autoimmune hepatitis is characterized by autoantibodies, hypergammaglobulinemia, and interface hepatitis on histological examination. The features lack diagnostic specificity, and other diseases that may resemble autoimmune hepatitis must be excluded. The clinical presentation may be acute, acute severe (fulminant), or asymptomatic; conventional autoantibodies may be absent; centrilobular necrosis and bile duct changes may be present; and the disease may occur after liver transplantation or with features that suggest overlapping disorders. The diagnostic criteria have been codified, and diagnostic scoring systems can support clinical judgment. Nonstandard autoantibodies, including antibodies to actin,  $\alpha$ -actinin, soluble liver antigen, perinuclear antineutrophil antigen, asialoglycoprotein receptor, and liver cytosol type 1, are tools that can support the diagnosis, especially in patients with atypical features. Prednisone or prednisolone in combination with azathioprine is the preferred treatment, and strategies using these medications in various doses can ameliorate treatment failure, incomplete response, drug intolerance, and relapse after drug withdrawal. Budesonide, mycophenolate mofetil, and calcineurin inhibitors can be considered in selected patients as frontline or salvage therapies. Molecular (recombinant proteins and monoclonal antibodies), cellular (adoptive transfer and antigenic manipulation), and pharmacological (antioxidants, antifibrotics, and antiapoptotic agents) interventions constitute future directions in management. The evolving knowledge of the pathogenic pathways and the advances in technology promise new management algorithms. (**Gut Liver 2016;10:177-203**)

**Key Words:** Diagnosis; Atypical phenotypes; Autoantibodies; Treatment

### INTRODUCTION

Autoimmune hepatitis has diverse clinical phenotypes, and this diversity has complicated its diagnosis and management.<sup>1-5</sup> The classical perception of autoimmune hepatitis as a chronic inflammatory liver disease that affects mainly young white women has been expanded,<sup>6-8</sup> and diagnostic boundaries now encompass patients of both genders<sup>9,10</sup> all ages,<sup>11-14</sup> and various ethnic groups.<sup>5,15</sup> Patients may have acute, acute severe (fulminant), or asymptomatic presentations; they may lack conventional serological markers; and they may have atypical histological features.<sup>1-5</sup> Autoimmune hepatitis must now be considered in all patients with acute and chronic hepatitis of undetermined cause, including patients with graft dysfunction after liver transplantation.<sup>16-18</sup>

Diagnostic criteria have been codified, and diagnostic scoring systems have been developed to supplement clinical judgment in difficult cases.<sup>19-21</sup> The repertoire of serological markers has been expanded to improve diagnosis, and investigational assays are evolving that may have prognostic implications.<sup>22-31</sup> Corticosteroids alone or in combination with azathioprine are the mainstays of treatment,<sup>17,18,32-34</sup> but regimens, involving calcineurin inhibitors, mycophenolate mofetil, and budesonide, have emerged from diverse clinical experiences as alternative frontline and salvage therapies.<sup>35-51</sup> Furthermore, the clarification of pathogenic molecular and cellular interactions have suggested new, testable, therapeutic interventions.<sup>34,52-60</sup>

The goals of this review are to describe the nonclassical clinical phenotypes of autoimmune hepatitis, present the diagnostic criteria that have been formalized for this disease, indicate the current and evolving serological repertoire, present guidelines for the administration of conventional treatment regimens, outline strategies for incorporating nonstandard drugs in the treatment of selected patients, and indicate the site-specific molecu-

Correspondence to: Albert J. Czaja

Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street S.W., Rochester, MN 55905, USA

Tel: +1-507-284-2691, Fax: +1-507-284-0538, E-mail: czaja.albert@mayo.edu

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lar, cellular and pharmacological interventions that constitute future directions in the management of this disease.

## NONCLASSICAL CLINICAL PHENOTYPES

### 1. Acute and acute severe (fulminant) hepatitis

An acute presentation occurs in 25% to 75% of patients with autoimmune hepatitis,<sup>61-65</sup> and an acute severe (fulminant) presentation, characterized by the development of hepatic encephalopathy within 26 weeks of disease discovery, occurs in 3% to 6% of North American and European patients (Table 1).<sup>66,67</sup> Each presentation can suggest an acute viral, toxic, or drug-induced liver injury, and each can delay recognition and proper treatment of autoimmune hepatitis.

Classical features of autoimmune hepatitis may be absent or less evident in patients with an acute severe (fulminant) presentation. Antinuclear antibodies (ANA) are undetected or weakly positive in 29% to 39% of patients,<sup>68,69</sup> and serum immuno-

globulin G (IgG) levels are normal in 25% to 39% of individuals (Table 1).<sup>25,69</sup> Centrilobular hemorrhagic necrosis and massive or submassive liver necrosis dominate the histological findings in 86% of patients.<sup>67,68</sup>

Central perivenulitis with a prominent lymphoplasmacytic infiltrate and interface hepatitis supports the diagnosis of autoimmune hepatitis in 50% to 90% of patients with acute liver failure,<sup>67</sup> and a histological assessment has been encouraged if liver tissue can be obtained safely.<sup>69,70</sup> Heterogeneous hypoattenuated regions within the liver can be demonstrated by unenhanced computed tomography in 65% of patients with autoimmune hepatitis and acute liver failure, and these findings are disease-specific.<sup>61,71</sup>

### 2. Asymptomatic presentation

Autoimmune hepatitis is asymptomatic in 25% to 34% of patients, and the diagnosis must be considered in all individuals with newly discovered mild liver test abnormalities (Table 1).<sup>72,73</sup>

**Table 1.** Nonclassical Phenotypes of Autoimmune Hepatitis at Presentation

Nonclassical phenotype	Features	Implications
Acute onset	Frequency, 25%–75% <sup>63,65</sup> Newly developed or exacerbated pre-existent disease <sup>61,63</sup>	Can resemble acute viral, drug-induced, toxic or ischemic injury <sup>61</sup> Responds well to standard treatment <sup>61,63</sup>
Acute severe (fulminant) onset	Frequency, 3%–6% <sup>66,67</sup> Onset encephalopathy ≤26 weeks <sup>61</sup> Classical features may be absent <sup>68</sup> Centrilobular necrosis in 86% <sup>67</sup> Lymphoplasmacytic infiltrates and interface hepatitis in 50%–90% <sup>67</sup> Heterogeneous hypoattenuated regions by unenhanced CT <sup>71</sup>	Can resemble acute viral, drug-induced, toxic or ischemic injury <sup>61</sup> Requires transplantation evaluation <sup>61</sup> Variable response to corticosteroids and possible complications (sepsis) <sup>61</sup>
Asymptomatic presentation	Frequency, 25%–34% <sup>72,73</sup> Histological features similar to symptomatic patients <sup>73</sup> Become symptomatic in 26%–70% <sup>72,73</sup> Survival without treatment possible <sup>72</sup>	Low frequency of resolution if untreated (12% vs 63%) <sup>74</sup> Lower 10-year survival if untreated than in treated severe AIH (67% vs 98%) <sup>74</sup> Consider treating all patients <sup>74</sup>
Autoantibody-negative phenotype	Scoring systems diagnostic, 19%–22% <sup>75</sup> Acute liver failure possible <sup>83,84</sup> Anti-SLA positive in 9%–31% <sup>26,83</sup>	Steroid-responsive, 67%–87% <sup>75,81</sup> Test for nonstandard antibodies <sup>75</sup> Exclude celiac disease <sup>89,90,93</sup>
Atypical histological patterns	Centrilobular necrosis in 29% <sup>94</sup> Bile duct injury or loss possible <sup>100,101</sup>	May reflect severity and acuity of AIH <sup>94</sup> or suggest other diagnoses <sup>102</sup>
Graft dysfunction posttransplant	Recurrent AIH, 8%–12% after 1st year <sup>122</sup> <i>De novo</i> AIH, 1%–9% within 9 years <sup>113</sup> Anti-GSTT1 common in <i>de novo</i> AIH <sup>128</sup>	Variable steroid response <sup>113</sup> Cirrhosis and graft failure possible <sup>113</sup> Retransplantation required, 23%–50% <sup>113</sup>
Overlap syndrome	Mixed features of AIH+PBC or PSC <sup>102,107</sup> “Paris criteria” for AIH+PBC <sup>105,135</sup>	Variable treatment response <sup>52,53</sup> Frequently treated with steroids+UDCA <sup>130</sup>

CT, computed tomography; AIH, autoimmune hepatitis; anti-SLA, antibodies to soluble liver antigen; anti-GSTT1, antibodies to glutathione-S-transferase T1; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Symptoms develop in 26% to 70% of patients within 2 to 120 months (mean interval, 32 months), and histological findings, including the frequencies of moderate to severe interface hepatitis (87% vs 93%), periportal fibrosis (41% vs 41%), and bridging fibrosis (39% vs 48%), are similar between asymptomatic and symptomatic individuals.<sup>73</sup>

Untreated patients with mild, asymptomatic, autoimmune hepatitis improve spontaneously less frequently (12% vs 63%,  $p=0.006$ ) and less completely than treated patients with severe symptomatic disease during  $77\pm 31$  months of observation,<sup>74</sup> and they have a lower 10-year survival (67% vs 98%,  $p=0.01$ ).<sup>74</sup> The uncertainty that mild autoimmune hepatitis remains mild compels the consideration of corticosteroid therapy in all patients with the diagnosis.

### 3. Autoantibody-negative phenotype

Patients with typical clinical and laboratory findings of autoimmune hepatitis may lack ANA, smooth muscle antibodies (SMA), and antibodies to liver kidney microsome type 1 (anti-LKM1) (Table 1).<sup>75-77</sup> The revised original scoring system of the International Autoimmune Hepatitis Group (IAIHG) has reclassified 34% of patients with cryptogenic chronic hepatitis as definite or probable autoimmune hepatitis in one European study,<sup>78</sup> and two North American studies have indicated that 19% to 22% of patients with cryptogenic hepatitis can be categorized as autoimmune hepatitis by the scoring system of the IAIHG<sup>79</sup> or by clinical judgment.<sup>80</sup> Lower frequencies of autoantibody-negative autoimmune hepatitis (1% to 5%) have been reported in other studies applying different diagnostic criteria.<sup>81,82</sup> Autoantibody-negative autoimmune hepatitis has been a cause of acute liver failure in 7% of British patients<sup>83</sup> and 24% of Japanese patients with acute severe (fulminant) presentations.<sup>84</sup>

Antinuclear antibodies and SMA may emerge later in the course of the disease;<sup>85,86</sup> or nonstandard autoantibodies may be detected and support the diagnosis.<sup>75</sup> Antibodies to soluble liver antigen (anti-SLA) occur in 9% to 31% of these patients;<sup>26,83,87</sup> atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) support the diagnosis in some patients;<sup>88</sup> and immunoglobulin A (IgA) antibodies to tissue transglutaminase or endomysium may implicate celiac disease as the basis for the liver dysfunction in other patients.<sup>89-93</sup> The absence of autoantibodies does not preclude the diagnosis of autoimmune hepatitis or a benefit from corticosteroid therapy.<sup>75,76,81</sup>

### 4. Atypical histological patterns

Interface hepatitis is the *sine qua non* of autoimmune hepatitis, but the spectrum of histological findings that can accompany interface hepatitis without invalidating the diagnosis is expanding.<sup>17</sup> Centrilobular zone 3 necrosis is present in 29% of patients with and without cirrhosis,<sup>94</sup> and it may disappear in sequential tissue examinations (Table 1).<sup>95</sup> Centrilobular necrosis may be an acute or acute severe form of the disease, or it may

reflect the spontaneous exacerbation of chronic disease.<sup>94,96,97</sup> Patients with centrilobular necrosis respond well to conventional corticosteroid therapy, and they may normalize serum aminotransferase levels more frequently than patients without this histological finding (95% vs 88%).<sup>94</sup>

Bile duct injury may also be present with interface hepatitis.<sup>98-100</sup> Biliary lesions that are isolated, unassociated with a cholestatic clinical syndrome, and unaccompanied by antimitochondrial antibodies (AMA) may constitute AMA-negative primary biliary cholangitis (PBC) or small duct primary sclerosing cholangitis (PSC).<sup>100-104</sup> Bile duct injury, including destructive cholangitis (florid duct lesions), in conjunction with AMA in patients with otherwise classical features of autoimmune hepatitis may constitute an overlap syndrome between autoimmune hepatitis and PBC.<sup>102,105-107</sup> Bile duct injury manifested by ductopenia, portal fibrosis, and portal edema suggests an overlap syndrome with PSC.<sup>102</sup>

### 5. Graft dysfunction after liver transplantation

Autoimmune hepatitis can recur or develop *de novo* after liver transplantation, and it should be considered in all transplanted patients with graft dysfunction (Table 1).<sup>108-113</sup> The frequency of recurrence ranges from 8% to 68%, depending in part on the performance of liver tissue examinations by protocol or by clinical indication.<sup>113-118</sup> Autoimmune hepatitis recurs in 8% to 12% after 1 year and 36% to 68% after 5 years (range, 2 months to 12 years after transplantation).<sup>113,119-122</sup> *De novo* autoimmune hepatitis occurs in 1% to 7% of patients (mainly children) 1 month to 9 years after transplantation for nonautoimmune liver disease.<sup>108,120,123-125</sup>

Diagnostic criteria for recurrent or *de novo* autoimmune hepatitis after liver transplantation have not been codified.<sup>113</sup> Most patients have hypergammaglobulinemia, increased serum levels of IgG, conventional autoantibodies, and interface hepatitis with or without portal plasma cell infiltration.<sup>119,126,127</sup> Adults with *de novo* autoimmune hepatitis may develop antibodies against glutathione-S-transferase T1 (anti-GSTT1).<sup>128</sup> Recurrent and *de novo* autoimmune hepatitis are variably responsive to conventional corticosteroid therapy; cirrhosis develops in as many as 60%; graft loss is possible; and retransplantation is required in 8% to 50%.<sup>113</sup>

### 6. Overlap syndromes

Patients with autoimmune hepatitis and features classically associated with PBC (AMA and histological features of bile duct injury or loss) and PSC (absence of AMA and cholangiographic changes of focal biliary strictures and dilations) have an overlap syndrome (Table 1).<sup>106,129,130</sup> Patients with autoimmune hepatitis may also have a cholestatic syndrome in the absence of classical features of PBC and PSC.<sup>99</sup> These patients may have an overlap syndrome with AMA-negative PBC or small duct PSC.<sup>102,103,107</sup>

The overlap syndromes occur in approximately 10% of pa-

tients with otherwise classical features of autoimmune hepatitis.<sup>107</sup> The major clinical consequence of the overlap syndromes is a variable response to conventional treatment regimens, and for this reason the diagnosis should be considered in all patients with refractory autoimmune hepatitis.<sup>106</sup> Treatment is empiric and based on weak clinical evidence. Corticosteroids in combination with low dose ursodeoxycholic acid (13 to 15 mg/kg daily) is a common management strategy endorsed by the major liver societies.<sup>105,130-132</sup>

The gold standard for the diagnosis is clinical judgment, and the strongest independent predictor of an overlap syndrome is the liver tissue examination.<sup>133,134</sup> The "Paris criteria" provide an objective basis for diagnosing the overlap syndrome between autoimmune hepatitis and PBC,<sup>105</sup> and they have a sensitivity of 92% and specificity of 97% compared to clinical judgment.<sup>135</sup>

## DIAGNOSTIC CRITERIA AND SCORING SYSTEMS

Formalized diagnostic criteria ensure the application of a standardized diagnostic algorithm,<sup>19</sup> and diagnostic scoring systems provide an evaluation template that can support the diagnosis in difficult cases.<sup>19-21</sup> All diagnostic guidelines recommend the performance of a liver tissue examination to establish the diagnosis.<sup>17,19,33,136</sup> Retrospective studies that propose elimination of the diagnostic tissue examination have failed to evaluate its importance in excluding patients with similar features but other diagnoses.<sup>137,138</sup>

### 1. Codified diagnostic criteria of the IAIHG

The diagnostic criteria of the IAIHG require the presence of compatible laboratory (serum aspartate [AST] and alanine ami-

**Table 2.** Comprehensive Diagnostic Scoring System of the International Autoimmune Hepatitis Group

Clinical features	Points	Clinical features	Points
Female	+2	Average alcohol intake (g/day)	
		<25	+2
		>60	-2
AP:AST (or ALT) ratio		Histologic findings	
<1.5	+2	Interface hepatitis	+3
1.5-3.0	0	Lymphoplasmacytic infiltrate	+1
>3.0	-2	Rosette formation	+1
		Biliary changes	-3
		Other atypical changes	-3
		None of above	-5
Serum globulin or IgG level above ULN		Concurrent immune disease, including celiac disease	+2
>2.0	+3	Other autoantibodies	+2
1.5-2.0	+2	HLA DRB1*03 or DRB1*04	+1
1.0-1.5	+1		
<1.0	0		
ANA, SMA, or anti-LKM1		Response to corticosteroids	
>1:80	+3	Complete	+2
1:80	+2	Relapse after drug withdrawal	+3
1:40	+1		
<1:40	0		
AMA positive	-4		
Hepatitis markers		Aggregate score pretreatment	
Positive	-3	Definite autoimmune hepatitis	>15
Negative	+3	Probable autoimmune hepatitis	10-15
Hepatotoxic drug exposure		Aggregate score posttreatment	
Positive	-4	Definite autoimmune hepatitis	>17
Negative	+1	Probable autoimmune hepatitis	12-17

AP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G; ULN, upper limit of the normal range; HLA, human leukocyte antigen; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, antibodies to liver kidney microsome type 1; AMA, antimicrobial antibodies.

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notransferase [ALT] abnormalities, hypergammaglobulinemia, and increased serum IgG level), serological (ANA, SMA or anti-LKM1 positivity) and histological findings (interface hepatitis with or without plasma cell infiltration).<sup>19</sup> Diseases that can resemble autoimmune hepatitis must also be excluded by appropriate tests, and these include virus-related, drug-induced, alcoholic, hereditary (Wilson disease, hereditary hemochromatosis), metabolic (nonalcoholic fatty liver disease [NAFLD]), and immune-mediated cholestatic diseases (PBC and PSC).<sup>19</sup> The designation of definite or probable autoimmune hepatitis reflects the level of confidence in the diagnosis based on the compatibility of the clinical features with classical autoimmune hepatitis. Two scoring systems are available for challenging cases.<sup>19,20</sup>

## 2. Revised original diagnostic scoring system of the IAIHG

The revised original scoring system is a comprehensive template that evaluates 13 clinical categories and renders 27 possible grades (Table 2).<sup>19</sup> This comprehensive scoring system was originally developed as a research tool by which to ensure the homogeneity of patient populations in clinical studies.<sup>139</sup> It has emerged subsequently as a template by which to ensure the systematic evaluation of patients, and it can serve as a mechanism by which to bolster clinical judgment.<sup>21,140</sup> The scoring system can accommodate deficiencies or inconsistencies in the clinical presentation and support the diagnosis in difficult cases by rendering a composite score before and after corticosteroid treatment.

## 3. Simplified diagnostic scoring system of the IAIHG

A simplified scoring system has been developed to ease clinical application.<sup>20</sup> It evaluates four clinical categories and renders

nine possible grades (Table 3).<sup>20</sup> The original revised scoring system has greater sensitivity for autoimmune hepatitis (100% vs 95%),<sup>21</sup> whereas the simplified scoring system has superior specificity (90% vs 73%) and accuracy (92% vs 82%), using clinical judgment as the gold standard.<sup>21</sup> The simplified scoring system does not grade the treatment response, and this difference may contribute to its lower sensitivity.<sup>141</sup> The revised original scoring system reclassifies patients with cryptogenic hepatitis as autoimmune hepatitis more commonly than the simplified scoring system (95% vs 24%), whereas the simplified scoring system excludes the diagnosis of autoimmune hepatitis more frequently in liver diseases that have concurrent immune manifestations (83% vs 64%).<sup>21</sup>

## 4. Limitations of the diagnostic scoring systems

The diagnostic scoring systems have been extensively evaluated and refined by retrospective analyses of patients that have been characterized in single medical centers and diagnosed by experts in autoimmune liver disease.<sup>20,21,140-143</sup> These characterizations have not followed a predefined protocol; pooled experiences have been limited; and comparative studies between medical centers have not been performed.<sup>141</sup> Furthermore, assessments have not always been uniform or complete in each patient.<sup>20</sup> Collaborative prospective clinical studies that adhere to a pre-established protocol and that ensure a uniform and complete assessment of each patient are necessary to validate the scoring systems.

The scoring systems have been applied beyond their original design and intention. They have been used inappropriately to determine the presence of autoimmune hepatitis in patients with PBC,<sup>144-146</sup> and this application has been discouraged.<sup>130</sup> The scoring systems have also been used but not validated in

**Table 3.** Simplified Diagnostic Scoring System of the International Autoimmune Hepatitis Group

Category	Scoring elements	Results	Points
Autoantibodies	ANA or SMA	1:40 by IIF	+1
	ANA or SMA	≥1:80 by IIF	+2
	Anti-LKM1 (alternative to ANA and SMA)	≥1:40 by IIF	+2
	Anti-SLA (alternative to ANA, SMA and LKM1)	Positive	+2
Immunoglobulins	Immunoglobulin G level	>ULN	+1
		>1.1 times ULN	+2
Histological findings	Interface hepatitis	Compatible features	+1
		Typical features	+2
Viral markers	IgM anti-HAV, HBsAg, HBV DNA, HCV RNA	No viral markers	+2
		Probable diagnosis	≥6
		Definite diagnosis	≥7

ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, antibodies to liver kidney microsome type 1; SLA, soluble liver antigen; IIF, indirect immunofluorescence; ULN, upper limit of the normal range; IgM, immunoglobulin M; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; HCV, hepatitis C virus; RNA, ribonucleic acid.

Adapted from Hennes EM, *et al.* *Hepatology* 2008;48:169-176, with the permission of John Wiley & Sons, Inc. and the American Association for the Study of Liver Disease.<sup>20</sup>

patients with acute severe (fulminant) liver failure<sup>141,147</sup> and in patients with graft dysfunction after liver transplantation.<sup>113</sup>

The performance parameters of the revised original and simplified scoring systems for autoimmune hepatitis are based on their compatibility with the gold standard of clinical judgment.<sup>19-21,140</sup> The results of these scoring systems can never supersede clinical judgment, and they cannot make a clinically untenable diagnosis tenable. Misapplication of the scoring systems and overinterpretation of their results are major pitfalls that must be avoided.

## SEROLOGICAL MARKERS

### 1. Standard autoantibodies

Antinuclear antibodies, SMA, and anti-LKM1 characterize most patients with autoimmune hepatitis, and they should be assessed in all candidates for the diagnosis (Table 4).<sup>17</sup> Antinuclear antibodies and SMA are usually present in the absence of anti-LKM1, and anti-LKM1 are usually detected in the absence of ANA and SMA.<sup>148,149</sup> This exclusivity has justified the designations of type 1 autoimmune hepatitis for those patients with ANA and/or SMA, and type 2 autoimmune hepatitis for those patients with anti-LKM1.<sup>148</sup>

The subtypes of autoimmune hepatitis have been associated with different age groups<sup>148</sup> and genetic predispositions,<sup>150-153</sup> but they have not been associated with major differences in treatment outcomes.<sup>17,33,154</sup> Accordingly, the subtypes have not been endorsed as valid pathological entities. Indeed, among adults with autoimmune hepatitis, there have been no significant clinical, laboratory, histological, genetic or outcome differences to justify a designation of type 1 and type 2 autoimmune hepatitis.<sup>155</sup>

### 1) Antinuclear antibodies and smooth muscle antibodies

Antinuclear antibodies and SMA lack disease- and organ-specificity (Table 4). Antinuclear antibodies are present in 80% of patients with autoimmune hepatitis, and SMA occur in 63%.<sup>156</sup> These antibodies also occur commonly in other liver diseases. Antinuclear antibodies are present in 20% to 40% of patients with alcoholic liver disease, NAFLD, chronic viral hepatitis, PBC or PSC.<sup>156-158</sup> Smooth muscle antibodies occur in 3% to 16% of patients with alcoholic liver disease, NAFLD, chronic hepatitis C, PBC or PSC.<sup>156-158</sup> Each autoantibody has low sensitivity for the diagnosis (32% for ANA and 16% for SMA) when present as an isolated finding.<sup>156</sup> The performance parameters of ANA and SMA are enhanced if both autoantibodies are present. The concurrence of ANA and SMA has a sensitivity of 43%,

**Table 4.** Standard Antibodies for the Diagnosis of Autoimmune Hepatitis

Standard antibodies	Antigenic target(s)	Clinical features
ANA	Centromere, ribonucleoproteins, ribonucleoprotein complexes, histones <sup>160,161</sup>	Lacks organ and disease specificity <sup>156</sup> Present in 80% of adults with AIH <sup>156</sup> Occurs in 20%–40% with non-AIH <sup>156-158</sup> Sensitivity for AIH when isolated finding, 32% <sup>156</sup> Specificity for AIH when isolated finding, 76% <sup>156</sup> Diagnostic accuracy for AIH, 56% <sup>156</sup> Concurrent ANA and SMA most diagnostic (74%) <sup>156</sup> Titers can vary outside disease activity <sup>86,156</sup>
SMA	Filamentous (F) actin, 86% <sup>162</sup> Nonactin components, 14% <sup>162</sup>	Lacks organ and disease specificity <sup>156</sup> Present in 63% of adults with AIH <sup>156</sup> Occurs in 3%–16% with non-AIH <sup>156-158</sup> Sensitivity for AIH when isolated finding, 16% <sup>156</sup> Specificity for AIH when isolated finding, 96% <sup>156</sup> Diagnostic accuracy for AIH, 61% <sup>156</sup> Concurrent SMA and ANA most diagnostic (74%) <sup>156</sup> Titers >1:80 associated with disease activity <sup>159</sup>
Anti-LKM1	Cytochrome P450 2D6 <sup>167,168</sup>	Present in 3% of North American adults with AIH <sup>149</sup> Detected in 14%–38% of British children with AIH <sup>11,163</sup> Occurs in 0%–10% of chronic hepatitis C <sup>156,164-166</sup> Low concurrence with SMA and ANA, 2% <sup>156</sup> High specificity (99%), low sensitivity (1%) <sup>156</sup> Diagnostic accuracy in North American adults, 57% <sup>156</sup>

ANA, antinuclear antibodies; AIH, autoimmune hepatitis; SMA, smooth muscle antibodies; anti-LKM1, antibodies to liver kidney microsome type 1.

specificity of 99%, and diagnostic accuracy of 74% for autoimmune hepatitis.<sup>156</sup>

Antinuclear antibodies seem to be the most variable marker during the course of the disease,<sup>86</sup> whereas SMA in titers >1:80 are associated with laboratory (77%) and histological (100%) activity.<sup>159</sup> Antinuclear antibodies are reactive against multiple nuclear components, including centromere, ribonucleoproteins, ribonucleoprotein complexes and histones, and 46% of patients with ANA have multiple nuclear reactivities.<sup>160,161</sup> Smooth muscle antibodies in autoimmune hepatitis are directed mainly against filamentous (F) actin, but nonactin reactivities are present in 14% of patients with SMA.<sup>162</sup>

## 2) Antibodies to liver kidney microsome 1

Antibodies to LKM1 are present in 3% of North American adults<sup>149,156</sup> and 14% to 38% of British children with autoimmune hepatitis (Table 4).<sup>11,163</sup> They can also be demonstrated in 0% to 2% of North American patients<sup>156,164</sup> and 10% of European patients with chronic hepatitis C.<sup>165,166</sup> Antibodies to LKM1 have a sensitivity of only 1% for autoimmune hepatitis in North American adults, but their specificity is 99% and their diagnostic accuracy is 57%. Only 2% of patients with ANA or SMA have anti-LKM1.<sup>156</sup> The cytochrome mono-oxygenase, P450 2D6, is the target antigen of anti-LKM1.<sup>167,168</sup>

## 2. Nonstandard autoantibodies

The nonstandard autoantibodies constitute a repertoire of serological markers that can support or extend the diagnosis of autoimmune hepatitis to highly selected individuals in whom the standard biomarkers are insufficient to render a diagnosis.<sup>169-171</sup> The presence of nonstandard autoantibodies can upgrade the diagnosis of autoimmune hepatitis by the revised original diagnostic scoring system of the IAIHG.<sup>17,19</sup>

### 1) Antibodies to actin

Antibodies to actin (antiactin) are directed against filamentous (F) actin, and they are present in 87% of patients with autoimmune hepatitis (Table 5).<sup>162,170,172</sup> They also occur in diverse immune-mediated, nonliver diseases, including systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, celiac disease, diabetes, autoimmune thyroiditis and Crohn's disease.<sup>170</sup> Antibodies to actin are a subset of SMA, and 86% to 100% of patients with autoimmune hepatitis and SMA have antiactin.<sup>162,173</sup> Both SMA and antiactin are indirect markers of laboratory and histological activity in autoimmune hepatitis.<sup>159</sup>

Most patients with antiactin have at least SMA or other conventional autoantibodies, and the detection of antiactin is not critical for the diagnosis.<sup>162</sup> Antibodies to actin have been associated with a higher frequency of death from hepatic failure or requirement for liver transplantation, but the prognostic implications of these antibodies are assay dependent.<sup>27,30,162,173-176</sup> Multiple assays for antiactin are available, but none has been

incorporated into a standard diagnostic repertoire.<sup>162,177</sup>

### 2) Antibodies to $\alpha$ -actinin

$\alpha$ -Actinins are cross-linking proteins that bind to actin and that are expressed as isoforms in muscle and nonmuscle cells.<sup>178</sup> Antibodies to  $\alpha$ -actinin have been found by enzyme-linked immunosorbent assay (ELISA) in 42% of patients with autoimmune hepatitis compared to 13% of patients with other liver diseases and 6% of healthy blood donors (Table 5).<sup>27</sup> Antibodies to  $\alpha$ -actinin are present in 66% of patients with autoimmune hepatitis who are positive for antifilamentous actin (anti-F actin), and the combination seems to be specific for the disease.<sup>27</sup>

Double reactivity to anti-F-actin and anti- $\alpha$ -actinin seems to have prognostic implications. Patients with both antibodies have clinical and histological activity and a severe form of the disease characterized by an acute onset.<sup>27</sup> Patients who respond to corticosteroid regimens have lower baseline levels of anti- $\alpha$ -actinin than patients who relapse or respond incompletely, and the baseline level of anti- $\alpha$ -actinin has been an independent predictor of treatment response.<sup>30</sup> The assay for anti- $\alpha$ -actinin is still investigational and not generally available.<sup>27,30</sup>

### 3) Antibodies to soluble liver antigen

Antibodies to soluble liver antigen (anti-SLA) are present in 7% to 22% of patients with autoimmune hepatitis, and their occurrence varies among different ethnic groups (Table 5).<sup>26,31,87,179,180</sup> Antibodies to soluble liver antigen seem to be least common in Japanese patients (7%)<sup>26</sup> and most common in German patients (19% to 22%).<sup>26,87</sup> The variability in serological expression may have a genetic basis, and anti-SLA have been associated with human leukocyte antigen (HLA) A1-B8 in Germany<sup>87</sup> and HLA DRB\*0301 in Britain<sup>25</sup> and the United States.<sup>24</sup>

Antibodies to soluble liver antigen have high specificity for autoimmune hepatitis (99%),<sup>179</sup> and they have been the sole marker of autoimmune hepatitis in 14% to 20% of patients who would otherwise have been classified as cryptogenic hepatitis.<sup>159,180,181</sup> They also have been associated with more severe histological findings, longer treatment requirement to suppress inflammatory activity, increased frequency of relapse after drug withdrawal, and higher frequency of liver transplantation or death from liver failure than patients without this marker.<sup>24-26,87,179</sup> The target antigen of anti-SLA is a transfer ribonucleic acid (RNA)-protein complex, now designated as SEPSECS (Sep [O-phosphoserine] tRNA:Sec [selenocysteine] tRNA synthase).<sup>23,182,183</sup> Antibodies to soluble liver antigen have also been closely associated with antibodies to ribonucleoprotein/Sjögren syndrome A antigen (anti-Ro/SSA), and the clinical implications of this tightly linked expression (96% concurrence) remains unclear.<sup>31,184-186</sup>

### 4) Atypical perinuclear antineutrophil cytoplasmic antibodies

Atypical pANCA are detected in 50% to 92% of patients

**Table 5.** Nonstandard Antibodies for the Diagnosis of Autoimmune Hepatitis

Nonstandard antibodies	Antigenic target(s)	Clinical features
Antibodies to actin (antiactin)	Filamentous (F) actin <sup>162</sup> Nonactin components <sup>162</sup>	Present in 87% with AIH <sup>162,170,172</sup> Concurrent with SMA in 86%–100% with AIH <sup>162,173</sup> SMA without antiactin in 14% with AIH <sup>162</sup> Indirect marker of disease activity <sup>159,162</sup> No standardized assay <sup>162,177</sup>
Antibodies to $\alpha$ -actinin (anti- $\alpha$ -actinin)	$\alpha$ -Actinin <sup>178</sup>	Present in 42% of patients with AIH <sup>27</sup> Antiactin+anti- $\alpha$ -actinin associated with severity <sup>27</sup> Baseline level predictive of treatment response <sup>30</sup> Investigational assay not generally available <sup>27,30</sup>
Antibodies to soluble liver antigen (anti-SLA)	Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase (SEPSECS) <sup>23,182,183</sup>	Present in 7%–22% with AIH <sup>26,31,87,179,180</sup> Genetic association with HLA DRB1*0301 <sup>24,25</sup> Associated with severity, response, relapse, survival <sup>24–26</sup> Useful in diagnosing seronegative patients <sup>159,180,181</sup> Specificity, 99%, and sensitivity, 11% <sup>179</sup>
Atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA)	$\beta$ -Tubulin isotype 5 <sup>189</sup>	Cross reacts with precursor bacterial protein (FtsZ) <sup>189</sup> Present in 50%–92% with typical AIH <sup>88,187–189</sup> Absent in anti-LKM1-positive AIH <sup>190</sup> Detected in CUC, PSC, PBC, minocycline injury <sup>188,191,193</sup> Useful in classifying seronegative AIH <sup>17,76,171,195</sup>
Antibodies to asialoglycoprotein receptor (anti-ASGPR)	Asialoglycoprotein receptor <sup>198,199</sup>	Present in 67%–88% with AIH <sup>28,198–201</sup> Occurs in other acute and chronic liver diseases <sup>198,203,204</sup> Useful in classifying seronegative AIH <sup>205</sup> Correlates with laboratory and histological activity <sup>206</sup> May predict relapse and define treatment end points <sup>201,206</sup>
Antibodies to liver cytosol type 1 (anti-LC1)	Formiminotransferase cyclodeaminase <sup>219–222</sup>	Present in 24%–32% of anti-LKM1-positive AIH <sup>208–210</sup> Occurs in chronic hepatitis C and anti-LKM1 <sup>211–214</sup> Useful in classifying seronegative AIH <sup>217,218</sup> Rare in North American adults with AIH <sup>216</sup>

AIH, autoimmune hepatitis; SMA, smooth muscle antibodies; HLA, human leukocyte antigen; anti-LKM1, antibodies to liver kidney microsome type 1; CUC, chronic ulcerative colitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis.

with autoimmune hepatitis, often in high titer (mean titer,  $11,410 \pm 1,875$ ),<sup>88,187–189</sup> and serum titers are not associated with laboratory tests of disease activity (serum AST, IgG, and  $\gamma$ -globulin levels).<sup>88</sup> Atypical pANCA exhibit some selectivity in that they are absent in anti-LKM1-positive autoimmune hepatitis,<sup>190</sup> but they can occur in chronic ulcerative colitis, PSC, PBC, chronic hepatitis C, and minocycline-induced autoimmune disease.<sup>187,188,191–193</sup>

The primary target antigen has been characterized as a 50 kDa protein on the inner side of the nuclear envelope,<sup>191</sup> and it has been identified as  $\beta$ -tubulin isotype 5.<sup>189</sup> Ninety-seven percent of patients with pANCA and autoimmune hepatitis have atypical pANCA, and 88% of the pANCA-positive patients have reactivity to  $\beta$ -tubulin isotype 5.<sup>189</sup> The pANCA of autoimmune hepatitis also cross-react with an evolutionary precursor bacte-

rial protein, FtsZ, and 82% of pANCA-positive patients with autoimmune hepatitis have reactivity to both proteins.<sup>189</sup> These dual reactivities have justified speculation that intestinal microorganisms trigger an immune response that results in liver inflammation in genetically susceptible individuals.<sup>189,194</sup>

The assessment of atypical pANCA has been included in the comprehensive diagnostic scoring system for autoimmune hepatitis,<sup>19</sup> and the autoantibodies may be useful in developing the diagnosis of autoimmune hepatitis in patients who are otherwise seronegative and classified as cryptogenic chronic hepatitis.<sup>17,76,171,195</sup> The presence of atypical pANCA has been associated with cirrhosis<sup>187</sup> and relapse after corticosteroid withdrawal in autoimmune hepatitis,<sup>196</sup> but the prognostic implications of atypical pANCA in autoimmune hepatitis have not been sufficiently established to warrant their routine assessment.<sup>17,88,197</sup>



### 5) Antibodies to asialoglycoprotein receptor

Antibodies to the asialoglycoprotein receptor (anti-ASGPR) are present in 67% to 88% of patients with autoimmune hepatitis (Table 5).<sup>28,198-201</sup> They occur in adults and children with autoimmune hepatitis, and they do not have an exclusive serological profile.<sup>202</sup> Antibodies to the asialoglycoprotein receptor can be present in acute hepatitis A (57%), acute hepatitis B (35%), PBC (14% to 100%), chronic hepatitis C (14%), alcoholic liver disease (8%), and chronic hepatitis B (7%).<sup>28,198,199,203,204</sup> The lack of disease specificity has compromised the diagnostic function of anti-ASGPR, and the major value of this serological marker may be in the assessment of patients who are seronegative for the conventional markers of autoimmune hepatitis.<sup>205</sup>

Antibodies to asialoglycoprotein receptor can disappear during corticosteroid therapy, and the disappearance has been associated with histological resolution.<sup>206</sup> Patients with anti-ASGPR during corticosteroid therapy also have a higher frequency of relapse after drug withdrawal than patients in whom anti-ASGPR has disappeared or never been expressed (88% vs 33%,  $p=0.01$ ).<sup>201,206</sup> These attributes suggest that anti-ASGPR may be useful in defining end points of treatment.<sup>28</sup> The inability to standardize the assay for anti-ASGPR has been the major limitation to its broad clinical application.<sup>28,199,201,207</sup>

### 6) Antibodies to liver cytosol type 1

Antibodies to liver cytosol type 1 (anti-LC1) co-exist with anti-LKM1 in 24% to 32% of patients with anti-LKM1-positive autoimmune hepatitis (Table 5).<sup>208-210</sup> They are also present in 12% to 33% of patients with chronic hepatitis C and anti-LKM1,<sup>211-214</sup> and they occur infrequently in patients with autoimmune hepatitis and SMA and/or ANA.<sup>215</sup> Antibodies to liver cytosol type 1 occur mainly in European children and young adults aged  $\leq 20$  years,<sup>209,210</sup> and they are rarely found in white North American adults.<sup>216</sup> Antibodies to liver cytosol type 1 may be the sole markers of autoimmune hepatitis in patients seronegative for SMA, ANA, and anti-LKM1,<sup>217,218</sup> but this diagnostic role may be limited, especially in North American adults in whom the frequency of anti-LC1 has been low.<sup>216</sup> Formiminotransferase cyclodeaminase is a cytosolic enzyme that has been identified as the target antigen of anti-LC1.<sup>219-222</sup>

## STANDARD DRUG REGIMENS

Prednisone or prednisolone alone or in combination with azathioprine is the mainstay therapy of autoimmune hepatitis (Table 6).<sup>17,33</sup> Combination therapy is preferred as lower doses of corticosteroid can be administered when combined with azathioprine, and the frequency of corticosteroid-related side effects is lower (10% vs 44%).<sup>223</sup> Both regimens have otherwise similar outcomes.<sup>223</sup> All patients with active autoimmune hepatitis are candidates for treatment regardless of symptom status (sym-

tomatic versus asymptomatic) or disease severity (mild versus severe).<sup>34,74</sup>

Combination therapy is appropriate for most patients, especially those with an anticipated low tolerance for corticosteroids (individuals with obesity, diabetes, hypertension, osteopenia, or emotional instability).<sup>34</sup> Monotherapy with corticosteroids is appropriate for patients with a known or anticipated intolerance of azathioprine (individuals with severe cytopenia [leukocyte count,  $<2.5 \times 10^9/L$ ; platelet count,  $<50 \times 10^9/L$ ], thiopurine methyltransferase deficiency [TPMT], or pregnancy) and for patients with acute severe autoimmune hepatitis or manifestations of acute liver failure.<sup>34</sup>

The immunosuppressive actions of azathioprine develop slowly over a 6-week period,<sup>224,225</sup> and monotherapy with prednisone or prednisolone may have a more rapid action than combination therapy in patients with acute severe disease.<sup>49</sup> Azathioprine is a category D drug for pregnancy in the United States, and congenital malformations have occurred in animal studies.<sup>226</sup> Furthermore, azathioprine metabolites can pass the human placenta,<sup>227</sup> and the drug has been of concern in the occurrence of human fetal complications.<sup>228</sup> These concerns have been strongly counterbalanced by numerous studies in azathioprine-treated women with inflammatory bowel disease in whom the rarity or nonexistence of azathioprine-related fetal complications has been documented.<sup>184,229-233</sup> Importantly, azathioprine is not an essential drug in the management of autoimmune hepatitis during pregnancy, and the drug can be replaced in pregnancy by an adjusted dose of prednisone or prednisolone.<sup>17,138</sup>

### 1. Combination therapy with prednisone or prednisolone and azathioprine

The preferred treatment regimen combining corticosteroids and azathioprine consists of an induction phase and a maintenance phase (Table 6).<sup>34</sup> During the 4-week induction phase, prednisone or prednisolone, 30 mg daily, is administered for 1 week. The dose is then reduced to 20 mg daily for 1 week and 15 mg daily for 2 weeks. Azathioprine, 50 mg daily, is given as a fixed dose during the entire induction phase. After 4 weeks of induction, the dose of prednisone or prednisolone is adjusted to 10 mg daily. The dose of azathioprine is maintained at 50 mg daily. The maintenance phase is continued at fixed doses of prednisone or prednisolone, 10 mg daily, and azathioprine, 50 mg daily, until normalization of serum AST, ALT, bilirubin, and  $\gamma$ -globulin or IgG levels and resolution of the histological abnormalities.<sup>17</sup> In Europe, prednisolone is preferred over prednisone, and it is commonly administered in a weight-based dose (up to 1 mg/kg daily) during the induction phase. Similarly, the dose of azathioprine is commonly weight-based (1 to 2 mg/kg daily).<sup>33,234,235</sup>

Blood leukocyte and platelet counts must be monitored throughout the induction and maintenance phases at 3 to 6

**Table 6.** Standard Drug Regimens for Autoimmune Hepatitis

Clinical situation	Combination therapy		Monotherapy
	Prednisone or prednisolone	Azathioprine	Prednisone or prednisolone
Treatment-naïve*	30 mg daily×1 wk <sup>17,18,34</sup>	50 mg daily fixed dose <sup>17,18,34</sup>	60 mg daily×1 wk <sup>17,18,34</sup>
	20 mg daily×1 wk		40 mg daily×1 wk
	15 mg daily×2 wk		30 mg daily×2 wk
	10 mg daily maintenance		20 mg daily maintenance
Treatment failure	30 mg daily×1 mo <sup>253,256</sup>	150 mg daily×1 mo <sup>253,256</sup>	60 mg daily×1 mo <sup>253,256</sup>
	20 mg daily×1 mo if improved	100 mg daily×1 mo if improved	Reduce dose by 10 mg for each
	10 daily maintenance if improvement continues	50 mg daily maintenance if improvement continues	month of improvement until 20 mg daily maintenance
	Increase dose to last level of improvement×1 mo if worsens	Increase dose to last level of improvement×1 mo if worsens	Increase dose to last level of improvement×1 mo if worsens
	Increase to 30 mg daily if worsening continues	Increase to 150 mg daily if worsening continues	Increase to 60 mg daily if worsening continues
Incomplete response	10 mg daily <sup>253</sup>	2 mg/kg daily <sup>253</sup>	20 mg daily <sup>253</sup>
	Dose reductions to maintain normal or near-normal liver tests with goal of drug withdrawal	Fixed dose as steroid dose reduced or discontinued with goal of indefinite azathioprine maintenance	Dose reductions to lowest dose possible to maintain normal or near-normal liver tests
Drug intolerance	Decrease dose or discontinue steroid <sup>17,253</sup>	Decrease dose or discontinue azathioprine <sup>17,253</sup>	Decrease dose or discontinue steroid <sup>17,253</sup>
	Increase azathioprine dose to 100 or 150 mg daily if necessary	Increase dose of steroid as needed or cautiously consider mycophenolate mofetil, 1–2 g daily <sup>41,45,46</sup>	Add azathioprine, 50 mg daily, and adjust dose
Relapse after drug withdrawal	Resume original regimen until resolution of liver tests	Resume original regimen until resolution of liver tests	Resume original regimen for until resolution of liver tests
	Gradually withdraw and discontinue as dose of azathioprine increased <sup>17,253</sup>	Increase dose to 2 mg/kg daily and continue indefinitely <sup>17,32,253</sup>	Decrease steroid dose to lowest level and maintain indefinitely <sup>17,253,259</sup>

\*Treatment-naïve regimens in Europe commonly include prednisolone at 1 mg/kg daily and azathioprine at 1–2 mg/kg daily.<sup>33,234,235</sup>

month intervals.<sup>17</sup> Progressive cytopenia warrants the reduction or discontinuation of azathioprine. The determination of TPMT activity prior to treatment can identify the 0.3% of the normal population with absent TPMT activity.<sup>236</sup> These patients are at risk for azathioprine-induced myelosuppression.<sup>138,237</sup> Routine genotyping or phenotyping for TPMT activity has not correlated closely with the occurrence of azathioprine toxicity except in those patients with absent enzyme.<sup>238–240</sup> Close monitoring of the clinical and hematological findings has been emphasized for all patients receiving this medication.<sup>17</sup>

## 2. Monotherapy with prednisone or prednisolone

Monotherapy with prednisone or prednisolone involves a 4-week induction phase and then a fixed-dose maintenance phase (Table 6).<sup>17</sup> During the 4-week induction phase, prednisone or prednisolone, 60 mg daily, is administered for 1 week. The dose is then reduced to 40 mg daily for 1 week and 30

mg daily for 2 weeks.<sup>34</sup> After 4 weeks of induction, the dose of prednisone or prednisolone is reduced to 20 mg daily, and the regimen is maintained until resolution of clinical, laboratory and histological findings.<sup>34</sup> An adjuvant program of regular weight-bearing exercise, vitamin D and calcium supplementation, and treatment with bisphosphonates (if justified by bone densitometry or clinical history of bone disease) may protect against progressive corticosteroid-related osteopenia.<sup>17</sup>

## 3. Treatment duration

Treatment is continued until normal laboratory tests and liver tissue.<sup>17</sup> Normal liver tests are achieved in 66% to 91% of patients within 2 years.<sup>138,235,241</sup> The average treatment duration until normal liver tests and normal or near-normal liver tissue is 22 months. Treatment may be extended for ≥3 years, but the frequency of remission decreases to 14% and progression to cirrhosis (54% vs 18%,  $p=0.03$ ) and need for liver transplanta-

tion (15% vs 2%,  $p=0.048$ ) increases compared to patients who respond fully within 12 months.<sup>242</sup>

In Europe, treatment is usually continued for at least 2 years before any decision regarding the discontinuation of therapy.<sup>235</sup> Histological improvement commonly lags behind clinical and laboratory improvement by 3 to 8 months, and treatment should be continued beyond laboratory resolution before any attempt at drug withdrawal.<sup>243</sup> Liver tissue examination is the preferred method of documenting histological resolution, but stable normal laboratory tests for 12 to 18 months may be sufficient to indicate the absence of histological activity and justify the termination of treatment.<sup>33</sup>

The decision to discontinue therapy must balance the possibility of a sustained long-term drug-free remission against the risk of relapse and the need for retreatment.<sup>244</sup> The frequency of achieving a treatment-free state is 19% to 40% in studies of at least 3 years duration<sup>80,245-248</sup> and 36% in studies of at least 5 years duration.<sup>248</sup> The frequency of relapse after drug withdrawal is 50% to 87% depending on duration of follow-up.<sup>246,249,250</sup> Relapse has been associated with progressive hepatic fibrosis in 10% and clinical deterioration in 3%, but in most instances relapse can be effectively treated with the prompt resumption of treatment.<sup>251</sup>

Ultimately, the decision to stop treatment must be based on patient preferences and the physician's ability to monitor for relapse and promptly restart treatment if necessary.<sup>244</sup> Drug withdrawal can be attempted under close monitoring, and the original treatment regimen can be rapidly resumed if serum aminotransferase levels increase. A rapid and complete response to retreatment can be anticipated (Table 6).<sup>249</sup> A long term maintenance regimen can then be instituted after normalization of liver tests by increasing the dose of azathioprine to 2 mg/kg daily and gradually withdrawing the corticosteroid.<sup>17,32</sup>

#### 4. Managing the suboptimal response

Liver tests worsen during therapy (treatment failure) in 7% of patients,<sup>252</sup> and they improve but not to normal levels (incomplete response) in 14%.<sup>242,253</sup> Treatment-ending side effects associated with corticosteroid therapy occur in 12% to 29%, and they are mainly intolerable cosmetic changes, obesity, emotional instability, and vertebral compression.<sup>74,245,254</sup> Treatment ending side effects associated with azathioprine therapy occur in 5% to 10% of patients, and they are mainly nausea, vomiting, rash, cytopenia ( $\leq 6\%$ ), pancreatitis, and liver toxicity.<sup>223,254,255</sup> Patients with cirrhosis develop corticosteroid-induced side effects more commonly than patients without cirrhosis (25% vs 8%) presumably because of increased systemic levels of unbound (free) prednisolone,<sup>48,223</sup> and they develop cytopenia that can suggest azathioprine toxicity more often (70% vs 26%,  $p<0.0001$ ).<sup>239,240</sup>

##### 1) Treatment failure

Patients who fail conventional treatment are treated with high

doses of the original medication (Table 6). The dose of prednisone or prednisolone is increased to 30 mg daily and the dose of azathioprine is increased to 150 mg daily.<sup>18,34,39,253,256</sup> Patients receiving monotherapy are treated with prednisone or prednisolone, 60 mg daily. Treatment is continued at a fixed dose for one month. Thereafter, the doses of medication are reduced by 10 mg of prednisone or prednisolone and 50 mg of azathioprine after each month of laboratory and clinical improvement until conventional maintenance levels for that particular regimen are reached.

The inability to improve tests after 1 month justifies continuation of the medication in unaltered dose. Worsening of clinical or laboratory status after a dose reduction warrants an increase in the dose to the last level associated with improvement, and the regimen should be maintained for another month until an improvement warrants another attempt at dose reduction. Clinical and laboratory features improve in 70% to 100% of patients; laboratory resolution occurs in 35%; and treatment withdrawal is possible in 20% to 35%.<sup>39,257</sup> Most patients remain on therapy indefinitely, and they are at risk for progression of their liver disease and the development of treatment-related side effects. Refractory progressive disease and manifestations of liver failure compel an evaluation for liver transplantation.

##### 2) Incomplete response

Patients who have not achieved clinical, laboratory and histological normality after 36 months of conventional treatment can be classified as having an incomplete response.<sup>242</sup> They are unlikely to achieve complete resolution with additional treatment, and the risk of drug-induced side effects increases. Management can be adjusted to prevent progression of the disease with the lowest tolerated dose of medication possible (Table 6). Therapy with prednisone or prednisolone, 10 mg daily, in combination with azathioprine, 2 mg/kg daily, can be started, and the doses can be gradually decreased to maintain a normal or near-normal serum AST level.<sup>253</sup> Treatment is indefinite, and the final regimen may consist of low dose corticosteroid in combination with azathioprine or monotherapy with dose-adjusted azathioprine or corticosteroid.<sup>32,258,259</sup>

##### 3) Drug-intolerance

Patients with drug-intolerance are treated by decreasing the dose of the toxic medication or discontinuing its use (Table 6).<sup>17,253</sup> The dose of the tolerated medication can be adjusted to suppress inflammatory activity. Mycophenolate mofetil (1 to 2 g daily) has been used for azathioprine intolerance, and it has successfully replaced azathioprine in 58% of cases.<sup>41,45,46,49,50</sup> Mycophenolate mofetil has side effects in 3% to 34% of patients, including cytopenia, which may resemble those of azathioprine, and it should be administered with caution or avoided in cytopenic patients.<sup>49,260,261</sup> It also has well documented teratogenic effects that preclude its use in pregnancy.<sup>262-265</sup>

## ALTERNATIVE DRUG REGIMENS

Budesonide, mycophenolate mofetil, and the calcineurin inhibitors (cyclosporine and tacrolimus) have been used as alternative frontline and salvage therapies in autoimmune hepatitis.<sup>34</sup> Budesonide has emerged mainly as an alternative frontline therapy in selected patients, whereas mycophenolate mofetil and the calcineurin inhibitors have been used mainly as salvage therapies.<sup>34</sup>

### 1. Budesonide as alternative frontline therapy

Budesonide (6 to 9 mg daily) in combination with azathioprine (1 to 2 mg/kg daily) has been shown by randomized clinical trial to normalize serum AST and ALT levels more frequently (47% vs 18%) and with fewer side effects (28% vs 53%) than conventional combination therapy with prednisone (40 mg daily tapered to 10 mg daily) and azathioprine (1 to 2 mg/kg daily) when administered for 6 months (Table 7).<sup>44</sup> The histological response has not been documented; the durability of the response is unclear; and the low frequency of laboratory response (18%) and high frequency of side effects (53%) in the patients receiving conventional corticosteroid therapy are unexplained. Nevertheless, budesonide, a next generation glucocorticoid, in combination with azathioprine has emerged as an alternative frontline treatment for autoimmune hepatitis.<sup>34</sup>

Subset analyses of children randomized to each regimen have disclosed similar frequencies of laboratory resolution (16% vs 15%) and side effects (47% vs 63%) between the budesonide and standard regimens.<sup>266</sup> For this reason, the superiority of budesonide therapy over standard treatment to induce remission in juvenile patients has been questioned.<sup>267</sup> These observations indicate that budesonide therapy can have variable effects in different populations and that careful patient selection may be

the key determinant of outcome.

Therapy with budesonide has been associated with the development of corticosteroid-induced complications in patients with cirrhosis,<sup>268,269</sup> break-through exacerbations of the liver disease during treatment that have required standard therapy,<sup>270</sup> and severe arthralgias and myalgias in patients previously treated with prednisone that have justified readministration of the standard drug regimen.<sup>271</sup> Combination therapy with budesonide and azathioprine may be most appropriate in treatment-naïve patients with mild liver inflammation, early stage disease, and absence of concurrent immune diseases. The presence of obesity, diabetes, hypertension, or osteopenia that might be worsened by prednisone treatment also support consideration of the budesonide regimen.<sup>34</sup>

### 2. Mycophenolate mofetil as frontline and salvage therapy

Mycophenolate mofetil, a next generation purine antagonist, has been used as a frontline and salvage therapy for autoimmune hepatitis.<sup>34</sup> As a frontline treatment in 59 patients treated for 3 to 92 months (mean, 26 months), mycophenolate mofetil (1 g daily adjusted to a final dose of 1.5 to 2 g daily) in combination with prednisolone (0.5 to 1 mg/kg daily followed by a tapered withdrawal) normalized serum ALT and  $\gamma$ -globulin levels in 88%, induced a partial laboratory improvement in 12%, allowed the withdrawal of corticosteroids in 58%, and induced treatment-ending side effects in 3% (Table 7).<sup>47</sup> Therapy with mycophenolate mofetil and prednisolone can be effective and safe in treatment-naïve patients, but comparative clinical trials with standard therapy are necessary to establish its preference.

Mycophenolate mofetil has also been used as a salvage therapy for patients with corticosteroid-refractory liver disease or azathioprine intolerance.<sup>34</sup> Composite analysis of the several, small, single center experiences indicates that mycophenolate

**Table 7.** Alternative Drug Regimens for Autoimmune Hepatitis

Clinical situation	Budesonide	Mycophenolate mofetil	Calcineurin inhibitors
Treatment-naïve	6–9 mg daily combined with azathioprine, 1–2 mg daily <sup>44</sup>	1.5–2 g daily combined with prednisolone, 0.5–1 mg/kg daily <sup>47</sup>	Cyclosporine, 2–5 mg/kg daily (trough, 100–300 ng/mL) <sup>36</sup>
Outcomes in juvenile AIH	Equivalent to standard therapy <sup>266</sup>	No established superiority over standard therapy <sup>34</sup>	Tacrolimus, 3 mg twice daily (serum level, 3 ng/mL) <sup>35</sup>
	Preferred in mild, noncirrhotic, uncomplicated AIH and patients with low steroid tolerance <sup>34</sup>		Equivalent to standard combination therapy and not preferred <sup>51,274,275</sup>
Treatment failure	Not effective in limited trial <sup>271</sup>	Effective in 23% <sup>34,50</sup>	Cyclosporine effective in 93% <sup>49</sup>
	Side effects with cirrhosis <sup>268,269</sup>	Avoid in pregnancy and severe cytopenia <sup>49,272,273</sup>	Tacrolimus effective in 87% <sup>38,276</sup>
			Low enthusiasm despite success <sup>49,277</sup>
Drug intolerance	Difficult to switch with prednisone without severe withdrawal symptoms <sup>271</sup>	Effective in 58% <sup>34,50</sup>	Limited use in steroid intolerance and associated with other complexities <sup>36,49</sup>
		Avoid in pregnancy and severe cytopenia <sup>49,272,273</sup>	

AIH, autoimmune hepatitis.

mofetil can induce improvement of laboratory tests in 45%, facilitate the withdrawal of corticosteroids in 40%, and cause treatment-ending side effects in 15% (Table 7).<sup>34,50</sup> Outcomes can be improved by using the treatment in a selective fashion. Therapy with mycophenolate mofetil has rescued patients who are azathioprine intolerant more commonly than patients who are refractory to conventional corticosteroid treatment (58% vs 23%),<sup>34,41,45,46,50</sup> whereas children with autoimmune hepatitis and sclerosing cholangitis have not responded.

Caveats that must be considered before instituting therapy include recognition that the drug is 6 to 7 times more expensive than azathioprine, treatment is commonly indefinite, side effects develop in 3% to 34%, and pregnancy is an absolute contraindication to its use.<sup>49,272,273</sup>

### 3. Calcineurin inhibitors as frontline and salvage therapies

Cyclosporine has been used successfully as a frontline agent in children and adults with autoimmune hepatitis,<sup>36,274,275</sup> but the only randomized clinical trial involving 39 patients has indicated equivalency rather than superiority of cyclosporine therapy to standard combination therapy (Table 7).<sup>51</sup> In the absence of clear advantages that outweigh the risks of treatment (hypertension, nephrotoxicity, infection, pancreatitis, neurotoxicity and malignancy) and its expense, frontline therapy with cyclosporine cannot be justified.<sup>49</sup> Similarly, tacrolimus (3 mg twice daily) has also had success as a frontline treatment in 21 patients who improved their serum ALT and AST levels after 3 months.<sup>35</sup> The cytopenia and nephrotoxicity that developed in these patients were not treatment-ending, but validation of this regimen by randomized clinical trial has not emerged after 20 years.

The calcineurin inhibitors have also been used successfully to salvage patients with corticosteroid-refractory autoimmune hepatitis.<sup>34</sup> Composite clinical experiences with cyclosporine in 22 such patients have indicated improvement of variable degree in 93% and failure of response due to recalcitrance, drug toxicity, or noncompliance in 7%.<sup>49,50</sup> Similarly, composite experiences with tacrolimus involving 44 patients have indicated improvement in 87% and failure of response in 13%.<sup>35,38,50,276</sup> The calcineurin inhibitors have been associated with serious side effects, including a paradoxical heightened state of autoreactivity, and endorsement of these agents as rescue therapies has not been universal.<sup>49,277</sup> Furthermore, the calcineurin inhibitors have mainly immunosuppressive rather than anti-inflammatory effects, and they have not been effective in preventing autoimmune hepatitis after liver transplantation.<sup>113,278</sup>

Treatment with the calcineurin inhibitors is commonly indefinite, and it requires experience to ensure careful monitoring and appropriate dose adjustment. Cyclosporine (Neoral) has been administered in doses of 2 to 5 mg/kg body weight with dose adjustments to achieve trough levels of 100 to 300 ng/mL,<sup>34,36,49</sup> and tacrolimus has been administered at a starting dose of 0.5

to 1 mg daily and increased to 1 to 3 mg twice daily as tolerated to achieve a serum level of 3 ng/mL (range, 1.7 to 10.7 ng/mL).<sup>34,35,38,49,276,279</sup>

### 4. Rapamycin, rituximab, and infliximab as emerging rescue drugs

Small clinical experiences with rapamycin (sirolimus), rituximab, and infliximab have illustrated the continuing effort that is being expended to develop rescue therapies that can supplant or supplement current corticosteroid-based regimens for autoimmune hepatitis.<sup>34,49,54,253</sup> Rapamycin (1 to 3 mg daily adjusted to maintain blood levels of 5 to 8 µg/dL) has suppressed the inflammatory manifestations of six patients with recurrent or *de novo* autoimmune hepatitis after liver transplantation, including five patients who were refractory to conventional corticosteroid treatment.<sup>280</sup>

Rituximab has improved isolated cases of autoimmune hepatitis with idiopathic thrombocytopenic purpura,<sup>281</sup> cryoglobulinemic glomerulonephritis,<sup>282</sup> previous B cell lymphoma,<sup>283</sup> and Evans syndrome (hemolytic anemia and idiopathic thrombocytopenia),<sup>284</sup> and rituximab (two infusions of 1,000 mg 2 weeks apart) has reduced serum AST levels in all six treated patients, improved histological features in four biopsied patients, and allowed corticosteroid withdrawal in three of four patients in a small treatment trial (Table 8).<sup>285</sup>

Similarly, a small trial of infliximab (infusions of 5 mg/kg body weight at time zero, 2 weeks, 6 weeks, and every 4 to 8 weeks thereafter) in 11 patients with refractory autoimmune hepatitis has normalized liver tests in eight patients, improved histological activity indices in five patients, and allowed treatment withdrawal in three patients (Table 8).<sup>55</sup> The development of side effects (mainly infectious complications) in seven of the 11 patients receiving infliximab, including three patients (27%) who required discontinuation of the drug, underscores the importance of establishing safety profiles, dosing guidelines, and monitoring strategies for each drug under trial before considering routine clinical application.<sup>286-291</sup>

## LIVER TRANSPLANTATION

Liver transplantation is the ultimate rescue therapy for patients that present with features of liver failure or who develop these features during standard treatment.<sup>256</sup> The 5- and 10-year patient survivals after liver transplantation exceed 70% in adults,<sup>118,292-294</sup> and the 5-year survival is as high as 86% in children.<sup>295</sup> Recurrent disease can progress to cirrhosis,<sup>296</sup> and 13% to 50% of adults with recurrent disease develop graft failure.<sup>115,297,298</sup> Retransplantation may be necessary with the understanding that autoimmune hepatitis may still recur.<sup>115,296</sup> Importantly, serious consequences of recurrent autoimmune hepatitis have not been uniformly experienced in all centers. The actuarial 5-year survivals for patients and grafts after re-

**Table 8.** Emerging Molecular, Cellular and Pharmacological Interventions for Autoimmune Hepatitis

Emerging interventions	Putative actions	Experience
<b>Molecular interventions</b>		
CTLA-4Ig (abatacept)	Disrupts CD28 binding to B7 ligands <sup>52</sup>	Approved for rheumatoid arthritis <sup>52</sup>
	Dampens T lymphocyte activation <sup>34,300</sup>	Improved murine model of PBC <sup>303</sup>
Anti-CD20 (rituximab)	Inhibits B lymphocyte activation <sup>53,300</sup>	Isolated patients with AIH <sup>281-284</sup>
		Effective in refractory AIH <sup>285</sup>
Anti-TNF- $\alpha$ (infliximab)	Inhibits TNF- $\alpha$ and interferes with maturation of cytotoxic T cells <sup>34,52</sup>	Effective in refractory AIH <sup>55</sup>
		Frequent side effects (27%) <sup>55</sup>
Nonmitogenic anti-CD3	Binds to antigen receptor of T cells <sup>300</sup>	Effective in diabetic model <sup>307</sup>
	Promotes apoptosis of immune cells <sup>34,53</sup>	Increases insulin in diabetic humans <sup>308</sup>
Anti-lysyl oxidase-like 2 (simtuzumab)	Inhibits lysyl oxidase and antifibrotic <sup>323</sup>	Phase 2 studies to prevent fibrosis in NAFLD and PSC ( <a href="https://clinicaltrials.gov">https://clinicaltrials.gov</a> )
	Prevents cross-linkage of collagen <sup>322</sup>	
<b>Cellular interventions</b>		
Adoptive transfer of regulatory T cells	Corrects deficiencies in cell population <sup>60</sup>	Effective in models of AIH <sup>56,312</sup>
	Expands immune regulatory population <sup>60</sup>	Effective in model of PBC <sup>313</sup>
Adoptive transfer of mesenchymal stromal cells	Affects innate and adaptive immunity <sup>60</sup>	Effective in models of RA <sup>301</sup>
	Inhibits B and T lymphocytes <sup>60</sup>	Promising in early human studies <sup>319-321</sup>
Modulation of natural killer T cells	Tailored glycolipid antigens skew dual immune actions favorably <sup>59,314,315</sup>	Effective in animal models of diabetes, RA, SLE and AIH <sup>300,316,317</sup>
<b>Pharmacological prospects</b>		
Antioxidants (N-acetylcysteine, S-adenosyl-L methionine)	Reduce reactive oxygen species <sup>322,323</sup>	Effective in NAFLD, chronic hepatitis C, and alcoholic cirrhosis <sup>324-327</sup>
	Decrease hepatocyte apoptosis <sup>322,323</sup>	
	Inhibit stellate cell activation <sup>322,323</sup>	
Angiotensin inhibitors (losartan)	Reduce profibrotic transformation of hepatic stellate cells to myofibroblasts <sup>322</sup>	Decreased fibrosis in chronic hepatitis C <sup>328</sup>

CTLA-4Ig, cytotoxic T lymphocyte antigen-4 fused with human immunoglobulin; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; NAFLD, nonalcoholic fatty liver disease; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

current autoimmune hepatitis have been 100% and 87% in one experience,<sup>115</sup> and patient and graft survivals have been similar to those of patients transplanted for nonautoimmune liver diseases in other experiences.<sup>118,297,299</sup> The risk of recurrent autoimmune hepatitis after liver transplantation should not affect the transplant decision. Liver transplantation is indicated by a model of end-stage liver disease (MELD) score >16 points, acute decompensation, intractable symptoms, treatment intolerance, or detection of liver cancer.<sup>293</sup>

## FUTURE DIRECTIONS

Most new therapeutic interventions have not moved beyond the theoretical stage in autoimmune hepatitis, but their premise and promise are founded on studies already performed in cell cultures, animal models, or preliminary clinical trials in other immune-mediated diseases.<sup>34,52,53,300,301</sup> They await rigorous study in autoimmune hepatitis.

### 1. Feasible molecular interventions

Monoclonal antibodies to tumor necrosis factor- $\alpha$  (infliximab)<sup>55</sup> and monoclonal antibodies to CD20 (rituximab)<sup>285</sup> have already begun an evaluation process in the treatment of autoimmune hepatitis (Table 8). Other molecular interventions that have advanced in animal studies and clinical trials outside autoimmune hepatitis also warrant consideration in this disease. Molecular interventions are intended to blunt or correct detrimental pathological mechanisms, but they may also interfere with normal homeostatic mechanisms and have unintended consequences. Their introduction as therapeutic agents requires an awareness of these possible consequences and rigorous evaluation in clinical trials.

Cytotoxic T lymphocyte antigen-4 fused with immunoglobulin (CTLA-4Ig) is a dimeric recombinant human fusion protein that is a homologue of the CD28 molecule expressed on the surface of CD4<sup>+</sup> T lymphocytes (Table 8).<sup>52</sup> CTLA-4Ig can interfere with the binding of CD28 with the B7 ligands (CD80 and CD86) expressed on antigen-presenting cells and prevent completion

of the signaling pathway necessary for lymphocyte activation.<sup>302</sup> CTLA-4Ig is already approved for use in rheumatoid arthritis, and it has improved the serological and histological manifestations of PBC in a murine model.<sup>303</sup>

Nonmitogenic monoclonal antibodies to CD3 target the T cell antigen receptor of T lymphocytes, and they can promote the apoptosis of immune cells (Table 8).<sup>300,304</sup> The newly released apoptotic bodies can then be ingested by macrophages and dendritic cells, and these cells can in turn produce transforming growth factor  $\beta$  (TGF- $\beta$ ).<sup>305</sup> Regulatory T cells that express the latency-associated peptide can be induced by TGF- $\beta$  and expand the immunosuppressive effect.<sup>306</sup> Antibodies to CD3 have already been shown to induce complete and durable remission in nonobese diabetic mice,<sup>307</sup> and clinical trials have demonstrated its effectiveness in maintaining or increasing insulin production in patients with insulin-dependent autoimmune diabetes.<sup>308</sup>

Simtuzumab (GS-6624) is a monoclonal antibody that is directed against the enzyme that promotes the cross-linkage of collagen fibrils and expansion of extracellular matrix (Table 8). Simtuzumab has been safe and well-tolerated in Phase 1 studies involving patients with hepatic fibrosis, and this monoclonal antibody to lysyl oxidase-like 2 has entered Phase 2 clinical studies designed to prevent hepatic fibrosis in NAFLD and PSC (<https://clinicaltrials.gov>, NCT01672853 and NCT016772879). The results of these trials will direct future applications of this preparation.

## 2. Feasible cellular interventions

Regulatory T cells and natural killer T cells are cell populations that help modulate immune reactivity, and they have been manipulated to suppress inflammatory and immune responses in animal models of diverse immune-mediated diseases (Table 8).<sup>59,300</sup> Regulatory T cells can be expanded by pharmacological agents (corticosteroids, rapamycin, mycophenolate mofetil, and 1, 25 dihydroxyvitamin D3)<sup>59</sup> or by the adoptive transfer of autologous cells that have been expanded or newly generated *ex vivo* and reintroduced.<sup>60</sup> Deficiencies in the number and function of regulatory T cells have been reported in autoimmune hepatitis,<sup>309,310</sup> albeit these findings have not been confirmed.<sup>311</sup> Despite the uncertainties, the adoptive transfer of regulatory T cells has been effective in a thymectomized neonatal mouse model of autoimmune hepatitis<sup>312</sup> and a murine model of autoimmune hepatitis based on immunization with the human antigens, formiminotransferase cyclodeaminase and cytochrome P450 D2.<sup>56</sup> Furthermore, adoptive transfer of these cells in a murine model of autoimmune cholangitis has reduced portal inflammation, bile duct damage, and the inflammatory response.<sup>313</sup> These experimental observations support the continued study of regulatory T cell expansion in the management of autoimmune hepatitis.

Natural killer T cells have stimulatory and inhibitory actions

on the innate and adaptive immune responses, and they are amenable to manipulation by antigenic stimuli that promote the desired predominant action (Table 8).<sup>59,300,314</sup> Natural killer T cells expressing a semi-invariant antigen receptor recognize glycolipid antigens bound to the CD1 antigen-presenting molecule, and glycolipid antigens can be designed to elicit the preferred action of these cells.<sup>315</sup> Natural killer T cells have been evaluated in animal models of type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, and autoimmune encephalomyelitis,<sup>300</sup> and studies in experimental autoimmune hepatitis have supported the further investigation of their pathogenic role and therapeutic implications in this disease.<sup>316,317</sup>

Mesenchymal stromal cells also affect the innate and adaptive immune responses by modulating the activity of macrophages, natural killer cells, and dendritic cells and by inhibiting the activity of B and T lymphocytes (Table 8).<sup>60</sup> The adoptive transfer of mesenchymal stromal cells has been effective in murine models of rheumatoid arthritis and radiation-induced liver injury,<sup>301,318</sup> and its therapeutic promise has been supported by preliminary human experiences in refractory Crohn's disease, corticosteroid-resistant graft-versus-host disease, and allograft rejection after kidney transplantation.<sup>319-321</sup> Serious side effects have not been encountered in mid-term human studies, but questions remain regarding the preferred expansion technique, the rare occurrence of immunogenicity in animal models, and the possible induction of chromosome aberrations, transient aneuploidy, or malignant transformations in cell cultures from murine and human sources.<sup>60</sup> There have been no reported experiences in autoimmune hepatitis.<sup>320</sup>

## 3. Pharmacological prospects

The generation of reactive oxygen species from Kupffer cells and myofibroblasts promotes the apoptosis of hepatocytes, the release of apoptotic bodies, and the activation of hepatic stellate cells.<sup>322,323</sup> Antioxidants (N-acetylcysteine, S-adenosyl-L-methionine, and vitamin E) have already been shown in clinical experiences to decrease histological activity, TGF- $\beta$  production, and fibrosis in NAFLD (Table 8).<sup>324,325</sup> They have also improved mortality in alcoholic cirrhosis,<sup>326</sup> and enhanced early viral responses in chronic hepatitis C.<sup>327</sup> Angiotensin inhibitors may inhibit the transformation of hepatic stellate cells into myofibroblasts, and losartan has decreased fibrosis in chronic hepatitis C.<sup>328</sup> The antioxidants and the angiotensin inhibitors are feasible antiapoptotic and antifibrotic agents that warrant evaluation as adjunctive therapies in autoimmune hepatitis.<sup>329-332</sup>

Agents that reduce apoptosis are feasible interventions in autoimmune hepatitis if their actions can be directed to the pertinent cell population. Caspase inhibitors have reduced apoptosis in murine models of acute liver injury,<sup>333</sup> bile duct ligation,<sup>334</sup> NAFLD,<sup>335</sup> and acute liver failure after massive hepatectomy.<sup>336</sup> They have also been used in limited clinical experiences involving patients with chronic hepatitis C<sup>337,338</sup> and NAFLD<sup>337</sup> and in

organs for liver transplantation to protect against ischemia/reperfusion injury.<sup>339</sup> The major concern is the possibility of unintended interference with normal apoptotic pathways that guard against the invasion of pathogens and the malignant transformation of cells.<sup>57</sup> Caspase inhibitors have not been evaluated in autoimmune hepatitis.

Patients with chronic liver disease, including autoimmune hepatitis, have reduced serum levels of 25-hydroxyvitamin D, and this deficiency has been associated with disease severity and hepatic fibrosis.<sup>340-345</sup> Vitamin D protects against oxidative stress, limits the proliferation of myofibroblasts, stimulates the expansion of regulatory T cells, reduces the production of pro-inflammatory cytokines, and modulates activation of immune effector cells.<sup>346-348</sup> Low serum levels of 25-hydroxyvitamin D may compromise these diverse beneficial actions, and vitamin D supplementation may be a measure to bolster actions that protect hepatocytes.<sup>349</sup> The impact of supplemental vitamin D therapy on the severity and responsiveness of corticosteroid-treated autoimmune hepatitis also requires evaluation.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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