Challenges in the diagnosis and management of autoimmune hepatitis

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BACKGROUND: Autoimmune hepatitis has diverse clinical phenotypes and outcomes that challenge current diagnostic criteria and management algorithms.
OBJECTIVES: To highlight the major difficulties in diagnosis and management, describe the efforts to ease them and encourage further progress in problem solving.
METHODS: The MEDLINE database was reviewed for published experiences from 1984 to 2013.
RESULTS: Acute or acute severe (fulminant) hepatitis, asymptomatic mild disease, and histological findings of centrilobular necrosis or bile duct injury can confound diagnosis and treatment. Continuation of conventional therapy until normal liver test results and liver tissue reduces the frequency of relapse, but does not prevent its occurrence. Problematic patients can be identified using mathematical models, clinical phenotype, serological markers and the speed of improvement after treatment; however, their recognition and treatment are inconsistent. Mycophenolate mofetil can rescue patients with azathioprine intolerance but is less effective for refractory disease. Budesonide in combination with azathioprine can be used frontline, but is effective primarily in noncirrhotic, uncomplicated disease. Molecular and cellular interventions are feasible but largely unevaluated.
DISCUSSION: Resolution of the current challenges requires revision of diagnostic criteria, characterization of biological markers that reflect pathogenic pathways, development of dynamic indexes based on changes in disease behaviour, and introduction of new pharmacological, molecular and cellular interventions that have undergone rigorous evaluation.
CONCLUSION: These challenges reflect important remediable deficiencies in current management.

Key Words: *Autoimmune; Challenges; Interventions; Nonstandard drugs; Phenotypes*

Les problèmes dans le diagnostic et la prise en charge de l'hépatite auto-immune

HISTORIQUE : L'hépatite auto-immune s'associe à des phénotypes cliniques et des issues variés qui remettent en question les critères diagnostiques et les algorithmes de prise en charge actuels.
OBJECTIFS : Faire ressortir les principaux problèmes de diagnostic et de prise en charge, décrire les efforts pour les atténuer et favoriser de nouveaux progrès dans la résolution de problèmes.
MÉTHODOLOGIE : Le chercheur a analysé la base de données MEDLINE pour obtenir les expériences publiées entre 1984 et 2013.
RÉSULTATS : L'hépatite aiguë ou aiguë sévère (fulminante), la maladie bénigne asymptomatique et les observations histologiques de la nécrose centrolobulaire ou d'une atteinte du canal cholédoque peuvent avoir une influence confusionnelle sur le diagnostic et le traitement. Le maintien du traitement classique jusqu'à l'obtention de tests hépatiques et de tissus hépatiques normaux réduit la fréquence des récidives, mais n'en prévient pas l'occurrence. On peut déceler les patients problématiques au moyen de modèles mathématiques, d'un phénotype clinique, de marqueurs sérologiques et de la vitesse d'amélioration après le traitement. Cependant, leur dépistage et leur traitement ne sont pas constants. Le mofétil de mycophénolate peut aider les patients présentant une intolérance à l'azathioprine, mais est moins efficace en cas de maladie réfractaire. Le budésonide associé à l'azathioprine peut être utilisé en première ligne, mais est surtout efficace en cas de maladie non cirrhotique et non complexe. Les interventions moléculaires et cellulaires sont faisables, mais largement sous-évaluées.
EXPOSÉ : Pour résoudre les problèmes actuels, il faut revoir les critères diagnostiques, la caractérisation des marqueurs biologiques qui reflètent les voies pathogènes, l'élaboration d'indices dynamiques fondés sur l'évolution du comportement de la maladie et l'adoption de nouvelles interventions pharmacologiques, moléculaires et cellulaires qui ont subi une évaluation rigoureuse.
CONCLUSION : Ces problèmes reflètent d'importantes lacunes de prise en charge qui peuvent être corrigées.

Autoimmune hepatitis has an evolving complexity that has generated multiple challenges in its diagnosis and management (1). These challenges reflect difficulties in recognizing its diverse clinical phenotypes, optimizing current corticosteroid regimens, identifying problematic patients early, incorporating new drug options into safe and effective management strategies, and developing new site-specific molecular and cellular interventions (2,3). Autoimmune hepatitis is no longer a disease that affects only young white women of European extraction, and antinuclear antibodies, smooth muscle antibodies, hypergammaglobulinemia and interface hepatitis no longer define all patients with this disease (4-6). Autoimmune hepatitis has a global distribution, and it affects all age groups and both sexes. It has diverse and unpredictable clinical manifestations, complex genetic predispositions, evolving treatment strategies and variable outcomes that are, in part, influenced by racial, socioeconomic, geographical and cultural factors (6).

A mindset fixed on a classical concept of autoimmune hepatitis is not sustainable because the clinical spectrum of the disease is expanding and the conventional therapies are being individualized according to particular phenotypic characteristics and treatment responses (7,8). Advances in the understanding of critical pathogenic pathways (9-11) and experiences in other immune-mediated diseases have identified opportunities to evaluate molecular and cellular interventions that promise to transform current management strategies and further diversify and individualize treatment options (3,12-15). The goals of the present review are to indicate the current challenges, describe the efforts to meet them, and encourage further progress in the diagnosis and management of this complex disease.

UNDERSTANDING THE DIVERSITY OF CLINICAL PHENOTYPES AT PRESENTATION

Autoimmune hepatitis may have an acute or acute severe (fulminant) presentation that challenges the diagnosis by resembling an acute viral or toxic hepatitis (16). It may have an asymptomatic presentation that challenges the need for treatment (17,18), and it may have histological findings of centrilobular (zone 3) necrosis (19-23) or bile duct

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TABLE 1
Diversity of clinical phenotypes at presentation

Phenotype at presentation	Features	Challenges
Acute onset or acute severe (fulminant) presentation	Abrupt onset at discovery, 25% to 75% (16,28)	Resembles acute viral or toxic hepatitis (16)
	Encephalopathy ≤26 weeks, 6% (16,29)	Absent classical clinical and laboratory features (31,33,34)
	ANA absent or weak, 29% to 39% (31,33,34)	Nonclassical histological findings (29,32)
	IgG normal, 25% to 39% (31,33,34)	Corticosteroid treatment versus LT (36,42)
	Centrilobular necrosis, 86% (20,29,32,35)	
	Low diagnostic scores (31)	
	Corticosteroid response, 36% to 100% (36)	
	Five-year survival rate after LT, 78% to 80% (40,41)	
Asymptomatic presentation	Frequency, 25% to 34% (17,18)	Uncertain need for treatment (18,43)
	Possible 10-year survival untreated (18)	Treatment risks, 14% (43)
	Moderate-severe lobular hepatitis, 91% (17)	Fluctuating disease severity and progression (17,43)
	Periportal and bridging fibrosis, 41% (17)	Late symptoms (17,18)
	Resolution untreated, 12% (43)	Immediate versus late treatment (17,43)
	Late symptoms, 26% to 70% (17,18)	
	Untreated 10-year survival, 67% (43)	
Centrilobular (zone 3) necrosis	Frequency, 29% (23)	Diagnostic confusion (16,23)
	Interface hepatitis present, 78% (20)	Resembles acute toxic, ischemic or drug-induced liver injury (16,29)
	Occurs in acute and chronic disease (23)	
Bile duct injury	Nondestructive cholangitis, 7% to 9% (44,46)	Distinguishing PBC, PSC or overlap syndrome (47)
	Destructive cholangitis, ≤5% (44,46)	Treatment strategy (corticosteroids alone or with ursodeoxycholic acid) (47)
	Isolated transient findings possible (24)	
	Overlap syndrome if cholestasis (45,47)	

Numbers in parentheses refer to references. ANA Antinuclear antibodies; IgG Immunoglobulin G; LT Liver transplantation; PBC Primary biliary cirrhosis; PSC Primary sclerosing cholangitis

injury (24,25) that challenge diagnostic dogma. These atypical phenotypes at presentation are outside the domains of current criteria for the disease (26,27); however, they must be recognized to ensure timely intervention.

Acute and acute severe (fulminant) presentations

Autoimmune hepatitis may have an acute onset, defined as an abrupt occurrence of symptoms and laboratory abnormalities coincident with disease discovery, in 25% to 75% of patients (16,28). It may also have an acute severe (fulminant) presentation, defined as hepatic encephalopathy within 26 weeks of disease discovery with or without cirrhosis, in 6% of patients (16,29) (Table 1). The acute onset may be due to an unsuspected chronic disease that has exacerbated spontaneously, newly formed severe disease, chronic disease with superimposed acute injury ('acute-on-chronic disease') or disease that has developed as an aftermath of liver transplantation (16,30).

The acuteness of the presentation may contribute to its variance from the classical phenotype of autoimmune hepatitis (Table 1). The serum immunoglobulin G level is normal in 25% to 39% of patients with acute and acute severe (fulminant) presentations; antinuclear antibodies are absent or weakly demonstrated in 29% to 39%; and serum γ-globulin levels and diagnostic scores by the international scoring system are lower than in classical chronic presentations (16,31-34). Centrilobular zone 3 necrosis, submassive hepatic necrosis or massive hepatic necrosis occur in 86% of patients with acute and acute severe (fulminant) autoimmune hepatitis (34), and the presence of interface hepatitis in most patients with centrilobular necrosis (20), especially in conjunction with plasmacytic infiltration or hepatocyte rosettes (32,35), typifies the histological features of acute-onset disease. Massive hepatic necrosis, centrilobular hemorrhagic necrosis with lymphoplasmacytic infiltration, lymphoid aggregates and plasma cell infiltration typify the histological features of acute severe (fulminant) autoimmune hepatitis (29).

Corticosteroid therapy is effective in 36% to 100% of individuals with acute or acute severe (fulminant) autoimmune hepatitis depending, in part, on the timeliness of diagnosis and treatment (36). Mortality has uniformly followed in these patients if there has been no improvement within two weeks of corticosteroid treatment, and they should be considered for liver transplantation (37). Oral prednisolone achieves a faster peak plasma concentration than oral prednisone (mean [± SD] 1.3±0.7 h versus 2.6±1.3 h), is not dependent on hepatic conversion to the active metabolite and has a systemic availability of 99±8% (compared with 84±13% for oral prednisone) (38,39). These attributes support a preference for prednisolone in the treatment of acute severe (fulminant) autoimmune hepatitis. Liver transplantation for acute liver failure in autoimmune hepatitis has a five-year survival rate of 78% to 80% (40,41) and the procedure should not be delayed in suitable candidates (36,42).

Asymptomatic autoimmune hepatitis

Autoimmune hepatitis may have an asymptomatic presentation in 25% to 34% of patients (17,18); the 10-year survival rate of untreated patients with this presentation may exceed 80% (18) (Table 1). This favourable outcome must be counterbalanced against its uncertainty and the risk of progressive liver disease. The frequencies of moderate-severe lobular hepatitis (91% versus 95%), periportal fibrosis (41% versus 39%) and bridging fibrosis (41% versus 48%) are similar in asymptomatic and symptomatic patients; 26% to 70% of asymptomatic patients become symptomatic (17,18). Furthermore, untreated asymptomatic patients improve less frequently than treated symptomatic patients with severe disease (12% versus 63%) and they have a lower 10-year survival rate (67% versus 98%) (43). The asymptomatic state at presentation does not preclude the need for treatment; the challenge is to develop an individualized management strategy that minimizes disease progression. The uncertainty that mild disease remains mild must guide the treatment decision; this uncertainty favours the treatment of all patients regardless of symptom status or disease severity at presentation (43).

Centrilobular necrosis and bile duct injury

Autoimmune hepatitis may have histological features of centrilobular (zone 3) necrosis (22,23) or bile duct injury (24,25,44,45); these findings challenge the classical pathological concepts of the disease (Table 1). Centrilobular necrosis is present in 29% of patients with

TABLE 2
Recommended adjustments in current treatment strategies

Treatment adjustments	Regimens	Challenges
Treatment until normal liver tests and liver tissue	Continue conventional treatment until serum AST, ALT, γ-globulin and IgG levels normal (49,60)	Preventing and treating drug intolerances (8,49)
	Maintain normal liver tests on treatment for three to eight months before liver biopsy (8)	Justifying liver biopsy before drug withdrawal (8)
	Normal liver tissue or inactive cirrhosis required before drug withdrawal (8,49)	Indefinite treatment possible (63)
	Discontinue prednisone alone or with azathioprine over six-week period (8)	Relapse, ≥20% (60,63,68)
	Monitor serum AST, ALT, γ-globulin levels every three weeks for three months, every three to six months for one year, then every six to 12 months thereafter (8,49)	
	Increase in serum AST or ALT level >3-fold ULN or γ-globulin level >2 g/dL indicates relapse (63)	
Long-term maintenance therapy after relapse	Restart original treatment until laboratory resolution (62,64)	Azathioprine intolerance (64)
	Increase azathioprine dose to 2 mg/kg as prednisone withdrawn (62,64)	Breakthrough exacerbation (64)
	Continue azathioprine at fixed dose (62,64)	Oncogenic and teratogenic risks (64,82)
	Use low-dose prednisone ≤10 mg daily if azathioprine intolerant (65,66)	Long-term corticosteroid treatment if azathioprine intolerance (65,66)

Numbers in parentheses refer to references. ALT Alanine aminotransferase; AST Aspartate aminotransferase; Ig Immunoglobulin; ULN Upper limit of normal range

autoimmune hepatitis regardless of the acuteness of the presentation, or the presence or absence of cirrhosis (23). Classical interface hepatitis is found in 78% of patients with centrilobular necrosis (20); this mixed histological pattern suggests a transition state between acute and chronic liver injury, an acute exacerbation of pre-existent chronic disease or an acute-on-chronic process (16). Sequential liver tissue examinations in patients with centrilobular necrosis have demonstrated spontaneous transformation from this pattern to that of classical interface hepatitis (20). This evolutionary sequence suggests that the centrilobular pattern is an acute early stage liver injury in patients without hepatic fibrosis and an acute superimposed liver injury in patients with hepatic fibrosis. Centrilobular necrosis is a dynamic histological pattern in autoimmune hepatitis, and does not implicate an etiological factor, characterize a particular clinical phenotype, or compel an alternative diagnosis or treatment (23).

Nondestructive lymphocytic or pleomorphic cholangitis is present in 7% to 9% of patients with classical autoimmune hepatitis (44), and fibrous cholangitis (44) or destructive cholangitis (florid duct lesion) (24,46) can be present in ≤5% (Table 1). Histological features of bile duct injury are outside the canon of autoimmune hepatitis (26); however, the occurrence of these coincidental background histological changes in the absence of clinical cholestasis does not detract from the diagnosis of autoimmune hepatitis or preclude conventional treatment (24). Concurrent findings of inflammatory bowel disease, an increased serum alkaline phosphatase level >2-fold the upper limit of the normal range, serum γ-glutamyl transferase level ≥5-fold the upper limit of the normal range, or numerous florid duct lesions on histological examination compel the performance of additional tests that include determination of serum antimitochondrial antibodies and endoscopic or magnetic resonance cholangiography (47). These studies may indicate that primary biliary cirrhosis (PBC), primary sclerosing cholangitis, or an overlap syndrome between autoimmune hepatitis and PBC or primary sclerosing cholangitis is the most appropriate diagnosis (47,48).

IMPROVING CURRENT TREATMENT REGIMENS

Prednisone (or prednisolone) alone (60 mg/day tapered each week to 20 mg/day over a four-week period) or a lower dose (30 mg/day tapered each week to 10 mg/day over a four-week period) in combination with azathioprine (50 mg/day, or 1 mg/kg/day to 2 mg/kg/day) is the standard treatment of autoimmune hepatitis (49). Treatment improves liver tests and liver tissue to normal or near normal in most patients within 24 months (50,51), prevents progressive hepatic fibrosis (52) and extends 10-year survival to 74% to 89% (53-57). The major management challenges are to achieve an optimal end point of therapy and to manage relapse after corticosteroid withdrawal.

Optimal end point of conventional corticosteroid therapy

Corticosteroid treatment should be continued until normalization of liver tests and liver tissue (Table 2) (49). Patients who sustain remission after corticosteroid withdrawal have significantly lower serum aspartate aminotransferase (AST), γ-globulin and immunoglobulin G levels immediately before histological examination and drug withdrawal than those who relapse (58-60). Liver tissue examination is best performed after normal laboratory tests have been maintained on treatment for three to eight months (7,8). Laboratory improvement lags behind histological resolution, and a protracted interval of continued treatment beyond test resolution increases the frequency of documenting histological resolution (8,61).

Histological examination is necessary to accurately classify the treatment response and direct the next action (8). Patients with incomplete histological resolution who exacerbate after treatment have been prematurely withdrawn from medication, and they should be retreated with conventional corticosteroid therapy until an optimal end point is achieved (62). Patients with complete histological resolution who exacerbate after drug withdrawal have relapsed (63), and they are candidates for long-term (indefinite) maintenance therapy with azathioprine (2 mg/kg/day) (7,8,49,62,64) or low-dose prednisone (≤10 mg/day) (8,65,66). The decision not to proceed with liver tissue examination reflects a willingness to manage responses empirically outside of guidelines (49) or a commitment to maintaining therapy indefinitely without expectation of drug withdrawal (67).

Management of relapse

Treatment until normal liver tests and liver tissue reduces the frequency of relapse after drug withdrawal but does not eliminate its occurrence (60). Patients treated to normal liver tests and liver tissue exhibit a frequency of relapse that is lower than that of patients treated to near-normal liver tests and liver tissue (20% to 40% versus 50% to 87%); however, they remain at risk for relapse and disease progression (60,63,68). Repeated relapses and retreatments are associated with progressive increases in the cumulative frequencies of cirrhosis (38% versus 4%) and requirement for liver transplantation or death from hepatic failure (20% versus 0%) compared with patients who sustain their remission after treatment (69). The challenge is to avoid the consequences of repeated exacerbations and retreatments; the institution of indefinite maintenance therapy after the first relapse meets this challenge (Table 2).

The preferred strategy after relapse is to start therapy with azathioprine (2 mg/kg/day) and to continue this treatment indefinitely (7,8,49,62,64). Conventional corticosteroid therapy is restarted after relapse to normalize the laboratory tests, then the corticosteroid

TABLE 3
Predictive prognostic features of autoimmune hepatitis (AIH)

Prognostic features	Implications	Challenges
Model scores	MELD score ≥12 points predicts treatment failure (sensitivity, 97%; specificity, 68%) (70) Unimproved UKELD predicts poor outcome (sensitivity, 85%; specificity, 68%) (71)	Not disease-specific (70,71) Low specificities for treatment failure (70,71)
Clinical phenotype	Young adults have HLA DRB1*03 more frequently than elderly patients (58% versus 23%) (72) Young adults often fail treatment (33%) (72) Elderly patients have cirrhosis (33%), HLA DRB1*04 (47%) and good response to therapy (72)	Lacks specificity (72) 'Blunt' prognostic tool (72) Routine HLA determinations discouraged (7,8,49)
Serological markers	Anti-SLA and relapse, 53% to 100% (76,77) Anti-SLA and HLA DRB1*03, 83% (76,78) Anti-SLA sensitivity for AIH, 7% to 19% (79) Anti-SLA specificity for AIH, >90% (77,79) Anti-actin and α-actinin occur with clinical and histological activity, 91% (81)	Anti-SLA infrequent in AIH (79) Anti-SLA vary by genotype (76,79) Absent anti-SLA not predictive (76) Need indices based on pathogenic pathways (cytokine levels, immune cell populations) (9)
Rapidity of treatment response	Failure to improve within 2 weeks indicates high mortality (37,71) Improvement within 12 months has less cirrhosis (18%) and need for liver transplantation (2%) (51) Elderly respond more quickly than young (51)	Requires time investment to assess response (37,51,71) No pretreatment predictors (8) Need dynamic indexes at each stage of disease (8,37)

Numbers in parentheses refer to references. HLA Human leukocyte antigen; MELD Model of End-stage Liver Disease; SLA Soluble liver antigen; UKELD United Kingdom Model for End-stage Liver Disease

component is withdrawn as the dose of azathioprine is increased to its weight-based level. Clinical and laboratory resolution is maintained in 83% of patients observed for 12 to 128 months (median 67 months), and the 10-year probability of a sustained clinical remission is 80% (8,64). Histological examinations disclose no or minimal inflammatory activity in 94% of patients; corticosteroid-induced side effects typically improve; and azathioprine is usually well tolerated (64). Arthralgias associated with corticosteroid withdrawal occur in 63%; lymphopenia develops in 8%; myelosuppression occurs in 7%; and diverse malignancies that reflect uncertain risk factors develop in 8% (8,64).

The long-term administration of low-dose prednisone (or prednisolone) is an alternative management strategy for patients with severe cytopenia or intolerance of azathioprine (65) (Table 2). Conventional corticosteroid therapy is restarted after relapse until clinical and laboratory resolution is achieved. The dose of prednisone (or prednisolone) is then reduced each month by 2.5 mg until instability in serum AST level is recognized. The corticosteroid dose is then increased by 2.5 mg to again stabilize the tests, and the new dose is maintained indefinitely (65). Eighty-seven per cent of patients can be managed on ≤10 mg/day of prednisone (median dose 7.5 mg/day); side effects associated with the original corticosteroid regimen improve or disappear in 85%; and new drug-related complications do not develop (65). Low-dose corticosteroid therapy has been maintained safely and successfully for seven to 43 years (median 13.5 years) (66). Low-dose corticosteroid therapy is not designed to induce histological resolution and the possibility of slow histological progression cannot be excluded.

IDENTIFYING PROBLEMATIC PATIENTS EARLY

The early identification of problematic patients is an ongoing management challenge, and mathematical models (70,71), clinical phenotype at presentation (72), serological markers (73,74) and responsiveness to treatment (51) have been used for this purpose with varying success (Table 3). The objectives have been to recognize individuals whose autoimmune hepatitis will worsen during conventional corticosteroid therapy and to allow early intervention with individualized salvage therapies. Dynamic indexes that assess changes in the tempo of the disease during treatment are emerging as important prognostic instruments in this effort (37,71).

Mathematical models at presentation

Patients who will fail treatment, die of liver failure or require liver transplantation can be identified at presentation by the Model for End-stage Liver Disease (MELD) (8,70) (Table 3). A MELD score of ≥12 points at presentation has a sensitivity of 97% and specificity of 68% for treatment failure (8,70). The King's College group has extended these observations by indicating that changes in the MELD score, MELD plus sodium score and the United Kingdom Model for End-stage Liver Disease (UKELD) score during conventional corticosteroid treatment is predictive of outcome in treatment-naive, jaundiced individuals with autoimmune hepatitis (71). Failure of the UKELD score to decrease by at least two points within seven days of treatment has a sensitivity of 85% and specificity of 68% for death from hepatic failure, need for emergency transplantation or requirement for second-line immunosuppressive medication (71).

Clinical phenotype at presentation

The clinical phenotype at presentation can also identify potentially problematic patients (Table 3). Individuals who are ≤30 years of age fail conventional corticosteroid therapy more frequently than individuals ≥60 years of age (24% versus 5%), and they harbour the human leukocyte antigen (HLA) DRB1*03 more often (58% versus 23%) (72). In contrast, individuals who are ≥60 years of age have cirrhosis more commonly at presentation (33% versus 10%), fail conventional corticosteroid treatment less frequently with increasing age and harbour HLA DRB1*04 more often (47% versus 13%) (72).

Treatment failure is uncommon in patients with HLA DRB1*04, possibly because the HLA DRB1*04 alleles encode antigen-binding grooves within the class II molecules of the major histocompatibility complex that accommodate self-antigens that trigger less vigorous immune responses (10). Alternatively, aging decreases the expression of HLA class II molecules and the activation of antigen-stimulated T cells (72); this 'immunosenescence' may favour the development of less severe disease in elderly patients that can progress indolently to cirrhosis and respond well to corticosteroids (10,72).

The clinical phenotype is a 'blunt' prognostic instrument, and it is mainly useful as an alert to possible management difficulties in young adult patients. An awareness of age-related distinctions in disease behaviour and treatment response can direct adjustments in monitoring schedules that accommodate these differences. The challenge is to

TABLE 4
Promising nonstandard drugs in autoimmune hepatitis (AIH)

Nonstandard drug	Drug attributes	Challenges
Mycophenolate mofetil	Purine antagonist (62,82)	Unlicensed for use in AIH (12,82)
	TPMT independence (15,82)	Expensive (6 to 7 times greater than azathioprine) (12,82)
	Response (overall), 45% (8,15)	Side effects, 3% to 34% (82)
	Response (AZP intolerance), 58% (8,15)	Category D drug (teratogenicity) (83)
	Response (refractory disease), 23% (8,15)	Limited target population (8,82)
	Corticosteroid sparing, 40% (8,15)	
Budesonide	Next-generation glucocorticoid (8,39,62)	Uncertain durability of response (84)
	Hepatic first-pass clearance ≥90% (39)	Unknown histological response (84)
	Metabolites devoid of toxicity (39)	Unexplained low frequency of resolution (18%) and high frequency of side effects (53%) with standard therapy (84)
	Large trial comparing budesonide and AZP with prednisone and AZP after six months (84)	Ineffective in steroid-refractory or steroid-dependent disease (85)
	Laboratory resolution more common (47% versus 18%) and side effects fewer (28% versus 53%) than standard therapy (84)	Concurrent immune-mediated diseases may flare (85)
		Side effects in cirrhosis (86)
		Limited target population (8,15,39)

Numbers in parentheses refer to references. AZP Azathioprine; TPMT Thiopurine methyltransferase

develop prognostic instruments that are superior to age and HLA phenotype in predicting outcomes (75).

Serological markers at presentation

The characterization of serological markers that have prognostic value is an ongoing challenge, and antibodies to soluble liver antigen (anti-SLA) and antibodies to actin and α-actinin are examples of the investigational effort to meet this challenge (73) (Table 3). Anti-SLA are present in 53% to 100% of patients who relapse after corticosteroid withdrawal (76,77), and 83% of patients with these antibodies harbour HLA DRB1*0301 (76,78). These associations suggest that anti-SLA may be surrogate markers of a genetic propensity for severe disease and long-term dependence on continuous corticosteroid therapy. Antibodies to SLA have high specificity for autoimmune hepatitis (>90%), but they occur in only 7% to 19% of patients with the disease (74,77,79). These antibodies illustrate the principal problem with current prognostic markers in that they are informative only when they are present.

Alpha (α) actinin is an immune-reactive region within filamentous (F) actin (80,81). F actin, in association with its α-actinin component, influences cell movement, survival and regeneration (80,81) and may, thereby, affect disease severity. Antibodies to α-actinin have a greater sensitivity (44% versus 19%), albeit lower specificity (84% versus >90%), for autoimmune hepatitis than anti-SLA, and they have a prognostic implication when they coexist with antibodies to F actin (anti-actin) (81). Untreated patients with antibodies to both actin and α-actinin exhibit clinical (91% versus 52%) and histological activity (91% versus 50%) more frequently and higher serum AST levels at presentation (328±760 U/L versus 125±219 U/L) than untreated patients without these antibodies (81) (Table 3).

The dual reactivities to actin and α-actinin have not yet been correlated with outcomes, but the low occurrence of both antibodies in autoimmune hepatitis (28%) suggests that their prognostic value will be limited unless their predictability is near-absolute (81). Direct assessments of the critical cytokine pathways that modulate antibody-dependent and cell-mediated mechanisms of liver cell injury and determinations of the number and function of immune cell populations that counter-regulate the autoreactive response may prove closer to the objective of identifying a useful prognostic instrument than the characterization of new antibodies (9).

Rapidity of treatment response

The rapidity of the response to conventional corticosteroid therapy can also identify problematic patients early (Table 3). Patients who have died within four months after presentation have been characterized by the presence of multilobular necrosis on histological examination and the inability to normalize or prevent worsening of at least one liver test abnormality within two weeks of corticosteroid treatment (37). Similarly, 85% of icteric patients with severe autoimmune hepatitis whose UKELD score does not improve by two points within seven days of corticosteroid treatment experience a poor outcome (71).

Problematic patients with less severe presentations can also be identified by the speed and degree of their improvement during treatment (51) (Table 3). Patients who improve to normal or near-normal liver tests and liver tissue within 12 months of conventional corticosteroid treatment exhibit a lower frequency of progression to cirrhosis (18% versus 54%) and liver transplantation (2% versus 15%) than patients who require continuous corticosteroid therapy for ≥36 months to achieve these same improvements (51). Elderly patients respond more quickly than young adults, and patients ≥60 years of age who do not respond within six months generate greater concern at this interval than patients ≤40 years of age (51). The rapidity of the treatment response must be monitored closely; the challenge is to develop individualized management strategies that maximize the speed and degree of improvement.

INCORPORATING NEW DRUGS INTO TREATMENT STRATEGIES

Mycophenolate mofetil and budesonide are emerging as new frontline and salvage therapies for autoimmune hepatitis (8,15). These drugs are unlicensed in the United States for use in autoimmune hepatitis, and their administration has been for off-label indications. The challenge is to incorporate them into safe and effective management strategies (Table 4).

Mycophenolate mofetil and budesonide are the most commonly used and reported nonstandard drugs that have been administered in autoimmune hepatitis, and are representative of an evolving treatment repertoire. Other pharmacological agents mainly used in rescue therapy include the calcineurin inhibitors (cyclosporine and tacrolimus) and rapamycin (12,13,15,62,82).

Mycophenolate mofetil

Mycophenolate mofetil is a next-generation purine antagonist that has been supported as a rescue agent in autoimmune hepatitis by 11 small single-centre experiences (8,15) (Table 4). A compilation of recent experiences indicates that the drug is effective in 45% of treated patients and ineffective or poorly tolerated in 55%. Patients treated for azathioprine intolerance improve more commonly than patients treated for corticosteroid-refractory liver disease (58% versus 23%) (8,15), and the optimal target population for this agent is small.

Treatment with mycophenolate mofetil has several drawbacks that must be considered (82). It is six to seven times more expensive than azathioprine; corticosteroids must be continued in most patients; treatment is indefinite; side effects occur in 3% to 34%; and it has

TABLE 5
Feasible site-specific molecular and cellular interventions in autoimmune hepatitis (AIH)

Intervention	Intervention attributes	Challenges
Monoclonal antibodies to CD3	Nonmitogenic (7,12,14)	Untried in AIH (12)
	Targets T cell antigen receptor (7,12,14)	Side effects (fever, anemia, rash, infection) (12)
	Promotes apoptosis, TGF-β release and regulatory T cell function (12,14)	
	Effective in diabetic patients (7,12,14)	
Monoclonal antibodies to CD20	Targets B lymphocytes (14)	Intravenous infusion required (89)
	Prevents autoantibody production and antibody-dependent cytotoxicity (14)	Leukoencephalopathy (14)
	Limits cytokine production, antigen presentation, and T cell activation (14)	Interstitial pneumonitis (14)
	Limited trials in AIH (14,62,89)	Virus reactivation (14)
		Bacterial infections (14)
Recombinant CTLA-4Ig	Blocks second costimulatory T cell signal (12,14)	Untried in AIH (3,2,14)
	Approved for rheumatoid arthritis (12,14)	
	Effective in animal model of primary biliary cirrhosis (90)	
Adoptive transfer of regulatory T cells	Modulate immune response (12,14)	Uncertain pathogenic mechanisms (correct T cell deficiencies or bolster effect) (91,92)
	Generate and maintain in cell culture (94)	
	Success in animal model of AIH (93)	
Tailored glycolipid antigen stimulation of natural killer T cells	Customized antigenic stimulation (96)	Untried in AIH (14)
	Modulate immune response (95)	Uncertain disease specificity (14)
	Effective in other immune diseases (96-98)	

Numbers in parentheses refer to references. CTLA-4Ig Cytotoxic T cell antigen-4 fused with immunoglobulin; TGF-β Transforming growth factor-beta

been classified as a category D drug in pregnancy (82). Severe cranial, facial and cardiac abnormalities have been described in human neonates born of treated mothers (83). Although the metabolism of mycophenolate mofetil is independent of the thiopurine methyltransferase pathway, it can still induce myelosuppression (82). Consequently, it should not be used in patients whose azathioprine intolerance is reflected by cytopenia.

Budesonide

Budesonide is a next-generation glucocorticoid with 90% first-pass hepatic clearance and metabolites devoid of glucocorticoid activity (39) (Table 4). Budesonide (6 mg/day to 9 mg/day) in combination with azathioprine (1 mg/kg/day to 2 mg/kg/day) normalized serum aminotransferase levels more commonly (47% versus 18%) and with fewer side effects (28% versus 53%) than the combination regimen of prednisone (40 mg/day tapered to 10 mg/day) and azathioprine (1 mg/kg/day to 2 mg/kg/day) when administered as frontline therapy for six months (84). Budesonide in combination with azathioprine is emerging as an alternative frontline treatment despite uncertainties regarding the frequency of histological resolution during treatment and the durability of the response. The challenge is to characterize its appropriate target population.

Treatment with budesonide also has caveats that must be considered (Table 4). Budesonide is not effective as a salvage therapy for corticosteroid-refractory disease, nor can it be switched with prednisone without incurring severe withdrawal symptoms (39,85). Concurrent immune diseases, such as vasculitis or synovitis, may exacerbate presumably because of the high first-pass hepatic clearance of the drug and its low systemic bioavailability (85). In contrast, typical corticosteroid-induced side effects can develop in patients with cirrhosis presumably because of decreased first-pass hepatic clearance of the drug and increased systemic bioavailability (86,87). Budesonide therapy appears to be best suited for treatment-naive, noncirrhotic patients with uncomplicated disease.

New drugs will continue to emerge in autoimmune hepatitis as the need for them persists, their putative actions have appeal and their availability is ensured. The great challenge is to develop a collaborative network of clinical investigators that can assess these new agents in a rigorous and timely fashion.

DEVELOPING SITE-SPECIFIC MOLECULAR AND CELLULAR INTERVENTIONS

Site-specific molecular and cellular interventions are now feasible in autoimmune hepatitis mainly because of successes already achieved in other immune-mediated diseases (3,12,14). These interventions include the use of monoclonal antibodies, recombinant molecules and manipulation of immune cells (Table 5). Each modality has had little or no application in autoimmune hepatitis, but its consideration as a treatment opportunity has been justified by the nature of its putative actions and its performance in other autoimmune diseases. The challenge is to establish the efficacy and safety of each modality.

Monoclonal antibodies to CD3 and CD20

Nonmitogenic monoclonal antibodies to CD3 target the T cell antigen receptor of liver-infiltrating cytotoxic T cells and induce their apoptosis (7,12,14) (Table 5). This treatment has already been used successfully in animal models and humans with type 1 diabetes and awaits study in autoimmune hepatitis. Monoclonal antibodies to CD20 can blunt clonal expansion of activated B cells, inhibit an antibody-dependent cytopathic process and influence the activation of T cells (14,88). Rituximab has already been used successfully in rheumatoid arthritis and isolated cases of autoimmune hepatitis (14,89) and awaits formal study in autoimmune hepatitis.

Recombinant molecules to CTLA-4Ig

Recombinant cytotoxic T lymphocyte antigen-4 fused with immunoglobulin (CTLA-4Ig) blocks the second costimulatory signal essential for immunocyte activation and can blunt the immune response (3,12,14) (Table 5). Abatacept is already approved for rheumatoid arthritis in the United States and Europe, and it has recently been shown to be effective in treating a murine model of experimental PBC (90). Abatacept also awaits study in autoimmune hepatitis.

Immune cell manipulations

Regulatory T cells and natural killer T (NKT) cells exert powerful inhibitory and stimulatory actions on the key cytokine pathways involved in the development of autoimmune hepatitis, and immune cell manipulation is an additional important treatment opportunity (3,14) (Table 5). Discrepancies regarding the means by which the regulatory T cells affect the severity of autoimmune hepatitis exist because deficiencies in the function and number of these cells in some

studies (91) have not been evident in other studies (92). Nevertheless, the adoptive transfer of regulatory T cells in a murine model of experimental autoimmune hepatitis has significantly improved the histological activity index of these animals (93), and this experience has strengthened the hypothesis that the adoptive transfer of fresh regulatory T cells may be beneficial (94). The adoptive transfer of regulatory T cells also awaits rigorous study in autoimmune hepatitis.

NKT cells can be stimulated by glycolipid antigens that have been tailored to elicit favourable cytokine responses in a disease-specific fashion (14) (Table 5). The marine sponge-derived glycosphingolipid α-galactosylceramide modulates the immune response of NKT cells (95), and modifications of the length and structure of the acyl chain of a synthetic α-galactosylceramide molecule can affect NKT activity and the severity of type 1 diabetes in nonobese diabetic mice (96). Structure-guided design of the triggering glycolipid antigen can customize the immune response to the individual as well as the disease. Furthermore, individualized adjustments in the duration of NKT cell stimulation will prevent excessive activity of these immune modulating cells and potentially deleterious effects while maximizing their benefit (96,97). NKT cell manipulation has already been used successfully in animal models of type 1 diabetes, lupus erythematosus and collagen-induced rheumatoid arthritis, and awaits study in autoimmune hepatitis (14,98).

OVERVIEW

Autoimmune hepatitis has multiple challenges in its diagnosis and management; these challenges are being met by ongoing clinical and investigational studies. Diagnosis has already been improved by recognizing the diversity of clinical phenotypes associated with autoimmune hepatitis (4,6). Current treatment strategies have been improved by requiring normal liver tests and liver tissue before drug withdrawal and instituting long-term maintenance therapy after the first relapse (7,8,49). Problematic patients can be identified early by scoring systems that reflect early prognosis (70,71), clinical phenotypes that reflect age and genetic predisposition (72), serological markers such as anti-SLA (73), and the rapidity and completeness of the response to conventional corticosteroid treatment (51). New drugs can now be considered as a rescue agent for azathioprine intolerance or refractory liver disease (mycophenolate mofetil) (8,15,82) or as a frontline therapy in noncirrhotic, treatment-naive patients with uncomplicated disease (budesonide) (84). Experiences with monoclonal antibodies (anti-CD3 and anti-CD20), recombinant molecules (recombinant CTLA-4Ig) and immune cell manipulations (regulatory T cells and NKT cells) in animal models and humans with immune-mediated diseases now identify feasible interventions that may further expand the therapeutic horizon (3,12,14).

These efforts to meet current diagnostic and management challenges in autoimmune hepatitis, in turn, generate new challenges that remain unaddressed. There is a need to revise current diagnostic criteria to accommodate patients with acute severe (fulminant) presentations (16) and cholestatic features (ie, overlap syndromes) (47). The efficacy and safety of current treatment regimens need to be improved by developing therapeutic ranges based on blood levels for each drug (1,8). Problematic patients must be identified using biological markers (autoantibodies, cytokine levels, and immune cell counts or function) or by dynamic indexes that correlate time-related changes in disease manifestations to outcome. New interventions must continue to be identified and evaluated, and should include agents that can strengthen current regimens, such as antioxidants (N-acetylcysteine and S-adenosylmethionine) (14,99,100), or that can rescue patients from corticosteroid-refractory disease (rapamycin, monoclonal antibodies to CD3 or CD20, abatacept, or adoptive transfer of regulatory T cells or NKT cells) (3,12-14). Challenges exist in autoimmune hepatitis because they reflect important deficiencies in current management, and they will continue to emerge as healthy consequences of progress.

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