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REVIEW

Difficult treatment decisions in autoimmune hepatitis

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Abstract

Treatment decisions in autoimmune hepatitis are complicated by the diversity of its clinical presentations, uncertainties about its natural history, evolving opinions regarding treatment end points, varied nature of refractory disease, and plethora of alternative immunosuppressive agents. The goals of this article are to review the difficult treatment decisions and to provide the bases for making sound therapeutic judgments. The English literature on the treatment problems in autoimmune hepatitis were identified by Medline search up to October 2009 and 32 years of personal experience. Autoimmune hepatitis may have an acute severe presentation, mild inflammatory activity, lack autoantibodies, exhibit atypical histological changes (centrilobular zone 3 necrosis or bile duct injury), or have variant features reminiscent of another disease (overlap syndrome). Corticosteroid therapy must be instituted early, applied despite the absence of symptoms, or modified in an individualized fashion. Pursuit of normal liver tests and tissue is the ideal treatment end point, but this objective must be tempered against the risk of side effects. Relapse after treatment withdrawal requires long-term maintenance therapy, preferably with azathioprine. Treatment failure or an incomplete response warrants salvage therapy that can include conventional medications in modified dose or empirical therapies with calcineurin inhibitors or mycophenolate mofetil. Liver transplantation supersedes empirical drug therapy in decompensated patients. Elderly and pregnant patients warrant treatment modifications. Difficult treatment decisions in autoimmune hepatitis can be simplified by recognizing its diverse manifestations and individualizing treatment, pursuing realistic goals, applying appropriate salvage regimens, and identifying problematic patients early.

Key words: Autoimmune hepatitis; Fulminant hepatitis; Salvage therapy; Treatment end points

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INTRODUCTION

Corticosteroid therapy is established as an effective treatment for autoimmune hepatitis[1-3]. It induces clinical, laboratory and histological remission in 80% of patients within 3 years[2,4]; the 10- and 20-year life expectancies of treated patients exceed 80%[5-7]; hepatic fibrosis is reduced or prevented in 79%[8,9]; and variceal hemorrhage, death from hepatic failure, and deteriorations warranting liver transplantation occur in less than 5%[10,11]. These successes are tempered by the development of severe treatment-related side effects in 13%[12,13], treatment failure in 9%[14], incomplete response in 13%[15], and relapse after drug withdrawal in 50%-86%[2,4,16-18]. Efforts are ongoing to improve results by refining current treatment strategies[19] and by introducing different pharmacological agents, such as cyclosporine[20], tacrolimus[21,22], mycophenolate mofetil[23,24] and budesonide[25,26]. The benefits

from these efforts have not been fully realized, and the management algorithm is still in flux.

Treatment decisions in autoimmune hepatitis are complicated by the diversity of clinical presentations associated with the disease, uncertainties about the natural history of asymptomatic mild disease, evolving recommendations regarding treatment end points, varied nature of individuals refractory to or intolerant of the conventional therapy, and plethora of alternative immunosuppressive agents[27-30]. Diagnostic and therapeutic guidelines have been promulgated to codify the recognition and treatment of autoimmune hepatitis, but clinical judgment remains the essence of successful therapy[31,32]. Decisions to start or withdraw medication, manage a sluggish or absent response, and institute unfamiliar empirical therapy in problematic patients are difficult because they are highly individualized and not amenable to rigorous study.

In this review, the difficult treatment decisions in autoimmune hepatitis are described and the bases for making a sound judgment are provided. Treatment decisions can be guided but not codified, and every management strategy must be directed by the status of the individual patient.

Table 1 Conventional corticosteroid treatment regimens for autoimmune hepatitis[19,54,55]

Schedule	Monotherapy	Combination therapy	
	Prednisone only[1] (mg/d)	Prednisone[1] (mg/d)	Azathioprine (mg/d)
Induction period			
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Maintenance period			
Fixed doses until end point	20	10	50
Conditions that favor each regimen	Cytopenia (severe) Absent thiopurine methyltransferase activity Pregnancy Malignancy (active) Short trial (≤ 6 mo) Acute severe onset	Elderly/postmenopausal state Osteoporosis Brittle diabetes Obesity Acne Emotional instability/psychosis Hypertension Prolonged therapy (≥ 6 mo)	

[1]Prednisolone can be used in place of prednisone in equivalent doses.

DECISION TO TREAT ACUTE SEVERE (FULMINANT) HEPATITIS WITH CORTICOSTEROIDS

Autoimmune hepatitis can have an acute severe (fulminant) presentation[33-36], or a previously indolent chronic disease can exacerbate spontaneously and appear acute[37]. The diagnosis can be unsuspected if this propensity is not realized. Furthermore, the presence of centrilobular zone 3 necrosis on histological examination can suggest an acute viral or toxic injury[38-42]. The centrilobular zone 3 pattern can transform to the classical pattern of interface hepatitis as the disease evolves[39], and its presence early in the disease should not delay the diagnosis or therapy.

The key to recognizing acute severe autoimmune hepatitis is to remember it in the differential diagnosis and to make the designation after viral, drug-induced, toxic and metabolic disorders have been systematically excluded[31,43]. The diagnosis may include atypical histological findings (centrilobular zone 3 necrosis) or absent classical features (autoantibodies or hypergammaglobulinemia), but it is justified by the completeness of the exclusion effort[44,45].

Autoantibodies and hypergammaglobulinemia, especially increased serum IgG level, support the diagnosis of autoimmune hepatitis, but they are neither specific nor required for the diagnosis[31,45,46]. Seronegative patients can respond well to corticosteroid treatment, and those with severe presentations should not be denied this potential benefit because of their non-classical phenotype[47-50]. Confidence in the diagnosis can be enhanced by applying the comprehensive scoring system developed by the International Autoimmune Hepatitis Group (IAIHG)[31]. Atypical or absent classical features can be assessed in the context of other findings that may have sufficient strength to carry the diagnosis[46].

Corticosteroid therapy is effective in 36%-100% of patients with acute severe (fulminant) presentations[35,51,52], and this range of response may reflect in part the timeliness of treatment[53] (Table 1). The response to corticosteroid therapy should be evident quickly[56,57], and the failure of any laboratory test of liver inflammation to improve within 2 wk in a patient with acute severe disease is a justification for considering liver transplantation[53,56] (Table 2).

There are no clinical or laboratory features prior to therapy that reliably predict a treatment non-response[56], but the model of end stage liver disease (MELD) can be useful in assessing risk and quantifying improvement or deterioration. MELD scores ≥ 12 points at presentation have a sensitivity of 97% and specificity of 68% for treatment failure in autoimmune hepatitis, and patients with such scores warrant close scrutiny[14]. Infection has been associated with protracted corticosteroid therapy in patients with acute severe (fulminant) presentations[52], and treatment should be discontinued promptly whenever there is evidence that the disease is worsening or if there has been no improvement after 2 wk[53,56].

DECISION TO TREAT ASYMPTOMATIC MILD AUTOIMMUNE HEPATITIS

Autoimmune hepatitis may be asymptomatic in 25%-34% of patients[66,67], and 25%-85% of individuals can be clas-

Table 2 Difficult treatment decisions before starting conventional corticosteroid therapy

Problem	Response
Acute severe (fulminant) presentation	Prompt institution of conventional corticosteroid therapy with prednisone monotherapy[44,51-53] Azathioprine, 50 mg/d, can be added later if treatment is to be continued for ≥ 3 mo[55] Liver transplantation evaluation if laboratory indices worsen at any time during treatment, especially progressive hyperbilirubinemia, or no improvement after 2 wk[56]
Asymptomatic mild or mild disease	Institute conventional corticosteroid therapy with prednisone in combination with azathioprine[58,55] Consider empirical treatment with budesonide, 3 mg *tid*, in conjunction with azathioprine, 50 mg/d, if preexistent osteopenia, diabetes, hypertension, obesity, or emotional instability[25,26]
Autoantibody-negativity	Exclude viral, drug, toxic, metabolic causes and celiac disease[31,43] Apply codified scoring criteria of IAIHG for probable or definite diagnosis[31,46] Institute conventional corticosteroid therapy with prednisone in combination with azathioprine or a higher dose of prednisone alone[19,47-50]
Overlap syndromes	Conventional corticosteroid therapy alone or in combination with azathioprine if serum alkaline phosphatase level < 2 times ULN[59-62] Add ursodeoxycholic acid, 13-15 mg/kg per day, to corticosteroid regimen if serum alkaline phosphatase level ≥ 2 times ULN[60,63] Consider ursodeoxycholic acid alone, 13-15 mg/kg per day, if predominant features of PBC with minimal features of autoimmune hepatitis[64,65]

IAIHG: International Autoimmune Hepatitis Group; ULN: Upper limit of the normal.

sified as having mild disease by clinical, laboratory and histological findings[58,68,69]. Asymptomatic patients are typically men, and they have lower serum aspartate aminotransferase (AST) levels at presentation than symptomatic patients[66]. Histological features are similar between symptomatic and asymptomatic patients, including the occurrence of cirrhosis, and 26%-70% of asymptomatic patients become symptomatic during follow-up[66,67]. The asymptomatic state is meta-stable, and its presence does not exclude the existence of severe liver inflammation at presentation, especially in children, or its development later[58].

The natural history of mild autoimmune hepatitis is unknown, and patients with mild laboratory and histological disease can have 10- and 15-year survivals that exceeds 80% without treatment[67,70]. These results are better than those in untreated patients with severe disease, in whom the early mortality is 40%-50%[1-3], and they suggest that some patients with mild autoimmune hepatitis can do well without treatment. The difficulty is in identifying this safe population of patients. The lack of codified treatment guidelines and concerns about treatment-related side effects have resulted in highly individualized and inconsistent management strategies for these patients[30,58].

Untreated mild autoimmune hepatitis does not have a uniformly benign prognosis. Cirrhosis develops in 49% of untreated patients within 15 years[70]; liver failure and hepatocellular carcinoma are possible[58]; asymptomatic patients frequently become symptomatic[66,67]; and 10-year mortality exceeds 10%[67]. Spontaneous resolution is possible, but untreated patients with mild autoimmune hepatitis improve less commonly (12% *vs* 63%, $P = 0.006$) and more slowly than treated patients, and they have a lower 10-year survival (67% *vs* 98%, $P = 0.01$)[58]. The rapidity of improvement rather than the severity of inflammation may be important in preventing disease progression in mild disease, and protection can be most reliably obtained by instituting treatment[11].

Autoimmune hepatitis is by nature a labile and aggressive disease, and phases of mild disease activity can be interspersed with phases of severe activity that can be aggressive[71,72]. In this context, the true existence of mild autoimmune hepatitis can be questioned, and treatment criteria based on perceptions of disease severity at any single time point fail to recognize this fluctuating nature. The uncertainty that mild disease remains mild indefinitely favors therapy for all such patients. The urgency rather than the need for treatment may be all that is decreased in these individuals (Table 2).

Until randomized clinical trials are performed that compare treatment against no treatment, the management strategy in patients with mild autoimmune hepatitis should lean toward conventional therapy[58] (Table 1). This option eliminates concern regarding unsuspected disease progression, and the treatment response is likely to be rapid and well-tolerated.

DECISION TO TREAT AUTOANTIBODY-NEGATIVE AUTOIMMUNE HEPATITIS

Autoantibodies in autoimmune hepatitis are signatures of the disease, but they are not pathogenic or requisites for its occurrence[73]. They can appear and disappear during the illness[74]; they do not correlate closely with laboratory or histological indices of liver inflammation[74,75]; and they cannot be used to reliably monitor disease behavior[74,75]. Patients may have all the features of autoimmune hepatitis except the autoantibodies, and they can respond as well to corticosteroid therapy as patients with classical autoantibody-positive disease[47-50].

Seronegative individuals may have escaped detection by testing for the conventional autoantibodies, or their serological signature may be undiscovered. These patients may express conventional autoantibodies later in the course of their disease[74], or their diagnosis can be supported by testing for the non-classical autoantibodies, including antibodies to soluble liver antigen (anti-SLA)[76] and atypical anti-neutrophil cytoplasmic antibodies[77]. Celiac disease must also be excluded since celiac liver disease can have acute, acute severe (fulminant), and chronic presentations that may respond to gluten restriction[78-81]. IgA antibodies to tissue transglutaminase or

endomysium should be sought in all seronegative patients with active liver disease of undetermined cause[82-84] (Table 2).

Confidence in the diagnosis of autoantibody-negative autoimmune hepatitis can be strengthened by applying the comprehensive scoring system of the IAIHG[31]. Seronegative patients can frequently be categorized as having autoimmune hepatitis by this method[46]. Once the diagnosis has been made by the exclusion of other conditions that it might resemble, corticosteroid treatment should be started with regimens identical to those used in classical autoimmune hepatitis[19] (Table 1). Treatment should not be extended beyond 3 mo if there has been no improvement, and the accuracy of the original diagnosis and the legitimacy of the treatment regimen should be reassessed if the disease worsens despite compliance with the medication schedule.

DECISION TO TREAT OVERLAP SYNDROMES

Patients with autoimmune hepatitis may have findings that suggest concurrent primary sclerosing cholangitis (PSC)[85-87], primary biliary cirrhosis (PBC)[59,63,88,89], or a cholestatic syndrome in the absence of PSC and PBC[90,91]. Overlap syndromes lack codified clinical or pathological definitions, and they do not have a particular etiological agent or distinctive pathogenic mechanism[92,93]. The designations are arbitrary and imprecise, and the clinical phenotypes of patients with the same overlap designation are commonly different[60,92-96].

Twenty percent of patients with autoimmune hepatitis have antimitochondrial antibodies (AMAs)[61,97-100]; 19% have a disproportionate elevation of the serum alkaline phosphatase level[61]; 15% have increased serum levels of IgM[61]; 9% have histological features of bile duct injury[61,91,101,102]; and 8% have antibodies to the E2 subunit of the pyruvate dehydrogenase complex[103]. Any or all of these features suggest an overlap syndrome with PBC.

Similarly, 16% of patients with autoimmune hepatitis have concurrent inflammatory bowel disease[104,105]; 10% (adults) to 50% (children) have biliary changes reminiscent of PSC by magnetic resonance imaging or retrograde endoscopic cholangiography[106,107]; and 13% fail to respond to corticosteroids[14]. Any or all of these features suggest an overlap syndrome with PSC.

The overlap syndrome with PSC may be associated with intrahepatic bile duct changes (small duct PSC)[108,109] or extrahepatic bile duct changes with or without intrahepatic findings (classical PSC). Small duct PSC is probably an early stage of classical PSC as protracted follow-up demonstrates late involvement of the extrahepatic bile ducts in many patients[108,109]. The occurrence of intrahepatic biliary changes in patients with predominant features of autoimmune hepatitis could represent coincidental bile duct injury associated with the exuberant inflammatory process[90,91,102] or an overlap syndrome with small duct PSC or AMA-negative PBC[110].

The overlap syndromes are important because they are common, occur in 18% of adults with autoimmune liver disease, and they can respond poorly to corticosteroid therapy[62]. Adults with autoimmune hepatitis, ulcerative colitis and PSC by cholangiography enter remission less frequently during corticosteroid therapy than patients with normal cholangiograms (59% *vs* 94%, $P < 0.05$), and they fail treatment more commonly (41% *vs* 6%, $P < 0.05$)[104]. The inflammatory bowel disease is not a determinant of response since patients with ulcerative colitis and normal cholangiograms respond as well to corticosteroid therapy as counterparts without inflammatory bowel disease[104]. Cholangiography is important to make these distinctions, and it should be performed in all patients with autoimmune hepatitis and inflammatory bowel disease. Forty-two percent of these individuals will have biliary changes of PSC[104].

The variant syndromes should be suspected when patients with autoimmune hepatitis manifest clinical, laboratory or histological features of cholestasis or respond poorly to conventional corticosteroid therapy[62]. The serum alkaline phosphatase level is useful in distinguishing classical autoimmune hepatitis from its overlap syndromes with PBC and PSC[62]. Serum alkaline phosphatase levels more than fourfold higher than the upper limit of the normal (ULN) do not occur in classical autoimmune hepatitis, and the presence of an abnormality of this degree in a patient with other features of autoimmune hepatitis compels a search for underlying PBC or PSC[61]. In children, the serum γ glutamyl transferase (GGT) level is a more reliable indicator of cholestasis than the serum alkaline phosphatase level. Bile duct changes are common in advanced fibrotic liver disease regardless of type, and these biliary distortions detected by magnetic resonance imaging must be distinguished from PSC[111].

Management of the overlap syndromes is empirical and based on the predominant manifestations of the disease (Table 2). Adults with autoimmune hepatitis and features of PBC who have serum alkaline phosphatase levels less than twofold higher than ULN can be treated with corticosteroids[59,61,62]. Adults with higher serum alkaline phosphatase levels and those with florid duct lesions on histological examination are candidates for treatment with corticosteroids and ursodeoxycholic acid[63,112,113]. Ursodeoxycholic acid alone may be effective in some patients who have predominant features of PBC[64,65].

Adults with autoimmune hepatitis and PSC are commonly given a trial of prednisone and ursodeoxycholic acid[87], but in adults with mainly hepatitis features, corticosteroid therapy alone may be beneficial[86]. These patients typically respond less well to treatment than those with mixed features of autoimmune hepatitis and PBC[62,96]. Patients with the cholestatic syndrome in the absence of PBC and PSC can be treated with prednisone, ursodeoxycholic acid, or both depending on the serum alkaline phosphatase level[102]. Multicentered collaborative

investigations are needed to codify diagnostic criteria and establish confident treatment algorithms for these non-classical syndromes (Table 2).

The diagnosis of an overlap syndrome implies that its clinical phenotype is outside the boundaries of classical disease, but the point at which this occurs is unknown[94,113]. The features of the classical autoimmune liver diseases are not disease-specific, and they are commonly shared[62,88,114,115]. This commonality of manifestations can cluster in different densities in individual patients and suggest another disease. The overlap syndromes are probably atypical manifestations of a classical disease rather concurrent diseases or a distinctive pathological entity[92,94,113]. The diagnostic scoring systems of the IAIHG are not discriminative diagnostic indices, and they cannot be used to declare an overlap syndrome, especially because the definition of such an entity has not been codified[88,116,117].

DECISION TO STOP TREATMENT

Twenty-one percent of patients with autoimmune hepatitis achieve a sustained long-term remission after initial corticosteroid treatment, and 28% who relapse after drug withdrawal achieve this same result after retreatment[18]. Autoimmune hepatitis can enter a sustained inactive state after treatment[15,18,67,118], and this possibility has justified efforts to terminate therapy in all patients despite their well-recognized high frequency of relapse[17,72]. Patients who sustain their remission after drug withdrawal have fewer laboratory abnormalities at the time of drug withdrawal than patients who relapse, and the ideal treatment end point is when normal liver tests and tissue have been achieved[15,119-123] (Table 3).

The key laboratory indices to monitor are the serum AST, alanine aminotransferase, bilirubin and γ-globulin levels[121], and these tests should be normal prior to drug withdrawal. The ideal histological end points are normal liver architecture or inactive cirrhosis[15,123]. Relapse has been associated with residual plasma cell infiltration in the liver tissue despite the absence of other disruptive changes, and the plasma cells may indicate persistence of the immune response[119,123]. Plasma cell infiltration in the native liver has also been associated with recurrent autoimmune hepatitis after liver transplantation, and it may signal an active pathogenic process[134].

Liver tissue examination immediately prior to drug withdrawal is the only confident method of confirming an ideal treatment end point, but it should not be performed for at least 3 mo after normalization of the laboratory indices. Histological improvement lags behind clinical and laboratory resolution by 3-8 mo[2], and liver tissue examination before this interval will disclose histological features of interface hepatitis in 55% of instances[133].

The presence of interface hepatitis on the follow-up tissue examination justifies the continuation of therapy for an additional 6 mo before reconsidering drug withdrawal. Another liver tissue examination is not necessary if the histological findings 6 mo earlier have shown improvement during treatment and the inflammatory changes have been mild. The frequency of relapse after full resolution of the laboratory and histological features can be reduced from 86%[17] to 60%[121], and in some instances, as low as 20%[15].

Full resolution of liver tests and tissue is an ideal treatment end point, but it may be achievable in only 40% of patients[121]. Relentless pursuit of an ideal end point may be hazardous because the likelihood of a full response must be balanced against the risk of treatment related side effects[12,13]. Seventy-seven percent of patients who respond will do so within 24 mo, and patients aged ≥ 60 years respond more quickly than adults aged ≤ 40 years[11]. The rapidity of response may reflect age-related differences in the vigor of the immune response (immune senescence)[135-137] or human leukocyte antigen (HLA) status[138]. Elderly patients more commonly have

Table 3 Difficult treatment decisions during conventional corticosteroid therapy

Problem	Response
Determining treatment end point	Continue conventional therapy until normal serum AST, ALT, bilirubin and γ-globulin levels and normal liver tissue or inactive cirrhosis (ideal end point)[119-121] Continue conventional therapy until serum AST ≤ 2 times ULN, bilirubin and γ-globulin levels normal, and portal hepatitis or minimally active cirrhosis (satisfactory end point)[11,54,55] Decrease dose of culprit drug or discontinue its use if side effects emerge (drug toxicity end point)[13,55] Limit conventional corticosteroid treatment of patients aged ≥ 60 yr if an ideal or satisfactory end point has not been achieved ≤ 24 mo (incomplete response end point)[11,19,124,125]
Relapse after drug withdrawal	Institute original therapy until clinical and laboratory resolution, then increase azathioprine dose to 2 mg/kg per day as dose of prednisone is withdrawn[126,127] Continue daily azathioprine in fixed dose indefinitely[126,127] Use low dose prednisone (≤ 10 mg/d) if severe cytopenia (leukocyte counts < 2.5×10^9/L or platelet counts < 50×10^9/L) or other azathioprine intolerances[13,55] Use low dose prednisone (2.5-5 mg/d) to supplement azathioprine maintenance if abnormal serum AST level[55,128]
Treatment failure	Prednisone, 60 mg/d, or prednisone, 30 mg/d, in combination with azathioprine, 150 mg/d, for at least 1 mo, then dose reductions by 10 mg for prednisone and 50 mg for azathioprine each month of laboratory improvement until conventional doses reached[54,55,129] Evaluate for liver transplantation if minimal criteria for listing (MELD ≥ 15 points) are met[130-132]
Incomplete response	Azathioprine (2 mg/kg per day) indefinitely after corticosteroid withdrawal[54,55,127] Low-dose prednisone (≤ 10 mg/d) if azathioprine intolerance[54,55,128] Adjustments to maintain serum AST level ≤ 3 times ULN[55,133]

MELD: Model of end stage liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 4 Difficult treatment decisions after conventional corticosteroid therapy

Problem	Response
Empirical salvage drugs	Consider cyclosporine (5-6 mg/kg per day)[144-150] or tacrolimus (4 mg *bid*)[21,22,151,152] if progressive disease on conventional treatment Consider mycophenolate mofetil (1 g *bid*) if corticosteroid or azathioprine intolerance[23,24,153-159] Consider budesonide (3 mg *tid*) as frontline therapy if mild disease or if azathioprine maintenance insufficient after relapse or incomplete response[25,26] Complete benefit-risk and cost analyses before use[160,161] Empirical trial must not supersede liver transplantation[55,130,131]
Liver transplantation	Consider if acute severe (fulminant) presentation unresponsive or worse within 2 wk of conventional treatment[52,53,56,57] Consider if treatment dependent ⩾ 3 yr and features of decompensation develop (ascites, encephalopathy or variceal bleeding)[130] Consider if failure to conventional therapy and MELD score ⩾ 15 points[52,131,132]
Elderly patients (aged ⩾ 60 yr)	Restrict conventional therapy to combination regimen[124] Limit initial treatment to ⩽ 24 mo[125] Institute azathioprine maintenance therapy (2 mg/kg per day) if initial response is incomplete at 24 mo[124] Consider liver transplantation if features of decompensation emerge[132]
Pregnant patients	Counsel regarding risks of prematurity and infant mortality[162-167] Institute high-risk obstetrical care[30,162] Avoid azathioprine if possible[165,168] Reduce doses of prednisone to lowest levels to stabilize if not resolve laboratory indices[169] Reestablish conventional prednisone doses prior to delivery[169] Be alert to post-partum flares[163,164,169]

HLA DRB1*04 than young adults, and this phenotype has been associated with a quicker and better treatment response than other HLA phenotypes[138-142]. The inability to induce resolution within 24 mo of therapy portends the development of treatment-related side effects[13,143], and it justifies a change in the end point strategy.

Improvements during the initial 24 mo of therapy may still be sufficient to consider drug withdrawal despite the absence of an ideal response. The disappearance of symptoms, improvement of the serum AST levels to less than twofold greater than ULN, normalization of the serum bilirubin and γ-globulin levels, and histological improvement to portal hepatitis or minimally active cirrhosis have been associated with a sustainable remission for at least 6 mo in 50% of cases, and these improvements during therapy constitute a satisfactory but not ideal end point[16,72]. A protracted interval of quiescent disease that requires no therapy is a desirable achievement, and it may be long-term despite the absence of an ideal response. Discontinuation of therapy after achieving satisfactory milestones should be considered at the 24-mo interval or at any earlier point in the course of treatment if signs of drug intolerance have emerged[54,143] (Table 3).

Failure to achieve an ideal or satisfactory response by 24 mo requires reassessment of the individual clinical situation. Ninety-four percent of patients aged ⩾ 60 years who achieve an ideal or satisfactory end point do so within 24 mo[11], and those elderly patients who have not done so are best treated with a long-term maintenance strategy designed to reduce or eliminate the corticosteroid dose and replace it with azathioprine[126-128] (Table 4). Similarly, patients who have shown little improvement during this interval or who are manifesting corticosteroid-related side effects should be treated with long-term azathioprine maintenance[126,127] (Table 3).

In contrast, 36% of adults aged ⩽ 40 years achieve an ideal or satisfactory end point beyond 24 mo of therapy[11], and their original treatment regimen can be maintained for an additional 12 mo if they are drug tolerant. Eighty-one percent of the adults aged ⩽ 40 years who respond do so within 36 mo[11], and those who do not are candidates for maintenance therapy with azathioprine. Most patients with autoimmune hepatitis do relapse and require long-term maintenance treatment[4,16,18], but the patients who are able to achieve a sustained long-term remission should not be penalized by blanket consignment to continuous initial therapy[54].

DECISION TO TREAT AFTER RELAPSE

Relapse after drug withdrawal constitutes a recrudescence of inflammatory activity that is typified by the reappearance of interface hepatitis in the liver biopsy specimen[2]. Laboratory correlations with histological findings after drug withdrawal have indicated that an increase in the serum AST level to at least threefold higher than ULN is invariably associated with interface hepatitis, and liver tissue examination is not required to diagnose this occurrence[133].

Reinstitution of the original treatment schedule rapidly suppresses the exacerbation, and another clinical, laboratory and histological remission can be achieved[16]. Subsequent treatment withdrawal is typically followed by another relapse, and the sequence of retreatment, drug withdrawal, and relapse can be repeated indefinitely[16]. With each exacerbation and retreatment, the frequency of achieving a sustained remission decreases (14% after three retreatments)[16]; the occurrence of drug-related side effects escalates (70% after two retreatments)[12]; and the cumulative frequencies of progression to cirrhosis (38%) and liver failure increase (20%)[170]. The optimal time to prevent these outcomes is after the first relapse, and repeated administrations of the original treatment regimen are not advised.

The preferred management of relapse is to institute long-term treatment with azathioprine after the first exacerbation[126,127] (Table 3). Clinical and laboratory resolution is achieved with conventional corticosteroid

treatment, and then the dose of prednisone is gradually withdrawn as the dose of azathioprine is increased to 2 mg/kg daily. Azathioprine is then continued indefinitely as a maintenance therapy. Eighty-seven percent of patients are able to sustain clinical and laboratory remission in this fashion over 10 years[126,127]. The most common side effect is arthralgia associated with corticosteroid withdrawal (63%). Myelosuppression and lymphopenia occur in 7% and 57% of patients, respectively, and malignancies of diverse cell types and uncertain association with therapy have developed in 8%[127].

Prednisone in low dose can be used instead of azathioprine for long-term maintenance if there is preexistent or evolving cytopenia[128] (Table 3). The goal is to maintain the serum AST level below threefold greater than ULN on the least amount of medication. Eighty-seven percent of patients can be managed long-term on ≤ 10 mg/d prednisone (median dose, 7.5 mg/d)[128]. Observation intervals for up to 149 mo have indicated satisfactory outcomes that have justified continued application of the strategy. Side effects associated with the earlier conventional corticosteroid treatments improve or disappear in 85% of patients; new side effects do not develop; and survival is unaffected when compared with patients who receive standard dose corticosteroid therapy after relapse[128]. Recent studies in patients followed for as long as 43 years (median, 13.5 years) have confirmed that the low-dose prednisone strategy can be used effectively and safely in the long term[171].

DECISION TO TREAT THE ADVERSE RESPONSE

The unsatisfactory responses to initial corticosteroid therapy are treatment failure, incomplete response, and drug toxicity. Each adverse outcome justifies a treatment modification.

Treatment failure

Treatment failure connotes clinical, laboratory, and histological worsening despite compliance with the original treatment schedule[129]. Nine percent of patients fail treatment[14,15,129], and high-dose therapy with prednisone (30 mg/d) in conjunction with azathioprine (150 mg/d) or prednisone alone (60 mg/d) is the preferred initial approach to this problem[19,23,54,55] (Table 3). Doses of medication are maintained at this level for 1 mo before improvements in the laboratory tests justify an attempt at dose reduction. The dose of prednisone is reduced by 10 mg and the dose of azathioprine is reduced by 50 mg each month that the serum AST level improves, until the original conventional doses are reached[19,54,55]. Seventy percent of patients improve their clinical and laboratory findings within 2 years, but histological resolution is achieved in only 20%[129]. Most patients remain on therapy indefinitely. Manifestations of liver decompensation during high-dose therapy (encephalopathy, ascites, or variceal hemorrhage) are indications for liver transplantation[130].

Thirteen percent of patients have an incomplete response to conventional treatment[15,19,54,55]. The clinical, laboratory, and histological findings improve, but the improvements are insufficient to constitute an ideal or satisfactory end point. These patients are unlikely to enter remission if therapy is continued beyond 36 mo (< 3% occurrence)[11,130], and they are candidates for indefinite maintenance therapy with azathioprine alone[55,126,127] or low-dose prednisone[128,171] at that time (Table 3). Treatments should be adjusted to maintain the serum AST level below threefold greater than ULN if possible to reduce the likelihood of an aggressive histological lesion[133].

Drug toxicity

Drug toxicity compels dose reduction or premature discontinuation of the offending drug in 13% of patients[13]. Cytopenia, nausea, emotional lability, hypertension, cosmetic changes, and diabetes are typically dose-related, and these consequences can improve with dose reduction[55]. Severe reactions, including psychosis, extreme cytopenia (leukocyte counts < 2.5×10^9/L or platelet counts < 50×10^9/L), and symptomatic osteopenia with or without vertebral compression, justify immediate discontinuation of the offending agent[55]. In these patients, the single tolerated drug (prednisone or azathioprine) is continued in adjusted dose to suppress inflammatory activity. Routine phenotyping or genotyping for thiopurine methyltransferase deficiency has not been predictive of azathioprine-induced toxicity at the low doses of azathioprine (50-150 mg/d) used to treatment autoimmune hepatitis[172-174]. Accordingly, routine screening for this enzyme activity has not been established[13].

DECISION TO INSTITUTE EMPIRICAL SALVAGE THERAPY

Multiple immunosuppressive agents have emerged mainly from the transplantation arena, and they have site-specific actions of theoretical advantage in the treatment of autoimmune hepatitis[175-177]. Many such agents have been used empirically in small, single-institution, treatment trials with some success, and they have been proposed as salvage therapies[19]. None has been studied rigorously in controlled or comparative treatment trials; all must be used off-label in autoimmune hepatitis; and none has been incorporated into standard management algorithms. Target populations, dosing schedules, safety profiles and cost analyses are lacking, and the nature of the clinical situation that requires rescue is also unclear[153,160].

The major clinical problems that warrant rescue are worsening of the liver disease despite compliance with the standard corticosteroid regimen (treatment failure) and corticosteroid or azathioprine intolerance (drug

toxicity)[153]. In the former instance, the patient must be rescued from the liver disease, and in the latter instance, the patient must be rescued from the treatment. There are conventional corticosteroid- and azathioprine-based strategies for each of these contingencies, but new pharmacological agents have a theoretical basis and burgeoning experience that support their use[19,55].

The calcineurin inhibitor, cyclosporine, and the purine antagonist, mycophenolate mofetil, have generated the most interest (Table 4). Numerous studies have described successful salvage of patients with corticosteroid intolerance or treatment failure by administering cyclosporine[144-150], and similar results in fewer studies have been described with tacrolimus[21,22,151,152]. In a representative study, cyclosporine improved the laboratory tests of liver inflammation, reduced the histological activity index, and was well tolerated when administered for 26 wk[20].

Mycophenolate mofetil has induced clinical and laboratory improvements in 39%-84% of patients, and it has allowed discontinuation of corticosteroid treatment in most patients[23,24,151,154-159] (Table 4). Non-response or drug intolerance (nausea, vomiting, pancreatitis, rash, alopecia, deep venous thrombosis, and diarrhea) has been described in 34%-78% of patients treated with mycophenolate mofetil, and the potential benefits of this drug must be balanced against these deficiencies. Salvage therapy regardless of the drug is inconsistently effective, potentially toxic, interminable, and expensive[160]. Liver transplantation may offer the most reliable form of rescue, and it must be considered carefully as an alternative to empirical new drug therapy in every salvage situation[130] (Table 4).

The results of salvage therapy with cyclosporine, tacrolimus or mycophenolate mofetil can be improved by selecting the patients who are most likely to respond. The major reason for treatment failure with these agents is uncertainty about the correct target population and the proper timing, dosing and duration of treatment. Patients may advance quickly beyond drug rescue, and many patients may need a new liver rather than a new drug[53]. The ideal candidates for cyclosporine therapy are patients who have failed corticosteroid treatment or been intolerant of the conventional medications and who are still below minimal listing criteria for liver transplantation (MELD scores < 15 points)[131]. Transplantation should be considered at the first sign of liver decompensation (usually the development of ascites) during the new drug regimen[130] (Table 4).

Children with autoimmune hepatitis and cholangiographic features of sclerosing cholangitis (overlap syndrome) respond poorly to mycophenolate mofetil[24,178], as do adult patients who are failing conventional treatment[158]. Therapy with mycophenolate mofetil should be considered mainly in adults with azathioprine intolerance[158] and children with non-response to conventional corticosteroid regimens[24]. The metabolism of mycophenolate mofetil is independent of the thiopurine methyltransferase pathway, and it can be considered in patients with known thiopurine methyltransferase deficiency.

Budesonide has promise as an alternative frontline therapy in treatment-naïve patients with autoimmune hepatitis[25,179,180], but it has been variably successful as a salvage therapy in corticosteroid-treated patients with treatment failure or corticosteroid dependence[26,181]. Furthermore, it can be associated with glucocorticoid side effects, particularly in patients with cirrhosis and portosystemic shunting[161,181]. Similarly, treatment with ursodeoxycholic acid has not allowed consistent withdrawal from corticosteroid therapy or rescue from treatment failure[182].

DECISION TO TREAT THE ELDERLY

Twenty percent of adults with autoimmune hepatitis develop the disease after the age of 60 years[138,183,184], and these patients have a greater degree of hepatic fibrosis at presentation than young adults aged < 40 years[185] and higher frequencies of ascites[184] and cirrhosis[138]. These findings suggest that the elderly have aggressive liver disease that is commonly indolent and unsuspected. Symptoms of fatigue and myalgia may be attributed to the aging process; concurrent immune diseases, such as rheumatoid arthritis, may mask the underlying liver disease; and liver test abnormalities may be ascribed to the medications used for other ailments. The proper diagnosis may also trigger concern about side effects associated with corticosteroid therapy and result in reluctance to treat the condition in a standard fashion[186]. These concerns are justified, but they do not mitigate the need for treatment or portend a dismal outcome.

The indications for treatment and the initial treatment regimens are the same for the elderly as for young adults[124]. The preferred schedule is prednisone in combination with azathioprine (Table 1). Elderly patients enter remission as commonly as young adults (61% *vs* 59%), and they fail treatment less often (5% *vs* 24%, $P = 0.03$)[138]. Relapse, sustained remission, death from liver failure or need for liver transplantation occur as commonly in the elderly as in young adults[138], and the elderly respond more quickly to medication[11]. Patients aged ⩾ 60 years enter remission within 6 mo more frequently than adults aged < 40 years (18% *vs* 2%, $P = 0.02$), and most have achieved an ideal or satisfactory end point of therapy within 24 mo (94% *vs* 64%, $P = 0.003$)[11].

The development of side effects associated with medication relates mainly to the duration of initial therapy and the cumulative durations of subsequent corticosteroid treatment[125]. Protracted corticosteroid therapy for > 24 mo and retreatment with corticosteroids after multiple relapses must be avoided to reduce the occurrence of vertebral compression and progressive osteopenia[13]. The risk of treatment-related complications in the elderly underscores the importance of limiting corticosteroid therapy to < 24 mo. Azathioprine maintenance therapy (2 mg/kg per day) should be instituted if

treatment is to be extended beyond 24 mo or be required after the first relapse[30,124] (Table 4).

A bone maintenance regimen should also be prescribed for all elderly patients undergoing initial corticosteroid treatment[13,30,124]. Regular weight-bearing exercise should be emphasized, and calcium (1-1.5 g/d), vitamin D3 (400-800 U/d), and alendronate (70 mg/wk) should be considered as adjuvant therapies. An annual bone density assessment can guide the vigor of the bone maintenance schedule. Budesonide (3 mg *tid*) can be considered as an empirical supplement to long-term azathioprine maintenance if liver inflammation is controlled inadequately[19,124]. Liver transplantation is effective in rescuing elderly patients with liver failure who have been screened for other comorbidity. The 5-year survival after liver transplantation in carefully screened elderly patients is comparable to that of young adults (80% in patients aged 60-65 years and 73% in patients aged > 65 years *vs* 78% in patients aged 18-59 years). Elderly patients also have fewer episodes of acute cellular rejection[132].

DECISION TO TREAT PREGNANT WOMEN

Pregnancy complicates the management of autoimmune hepatitis because of the risks that the liver disease and its treatment pose for the mother and the fetus (Table 4). Perinatal mortality is 4%[162]; serious complications develop in 9%[163]; caesarian section is required in 17%; stillbirths occur in 5%; and fetal loss is 21%[164]. These outcomes are better than those in mothers with diabetes, but they do indicate the need for high-risk obstetrical care[164]. The presence of maternal antibodies to SLA and extractable nuclear antigens (Ro/SSA) is associated with a complicated course[163].

Azathioprine is associated with congenital malformations in pregnant mice, and it is a category D drug for pregnancy[165]. The odds ratio for having a child with congenital malformations while taking azathioprine for inflammatory bowel disease is 3.4, whereas it is negligible in similarly treated pregnant women with systemic lupus erythematosus[166]. There have been no reports of congenital malformations in the children of mothers treated with azathioprine for autoimmune hepatitis[166], and there have been no serious consequences associated with breast feeding of these infants[167]. Nevertheless, the placenta is only a partial barrier to the metabolites of azathioprine[168]; there have been no rigorously designed studies that confirm the safety of azathioprine in pregnant women with autoimmune hepatitis[166]; and azathioprine is not an essential medication in the management of the disease[19,30]. The preferred treatment during pregnancy is with prednisone alone.

Autoimmune hepatitis can improve during pregnancy possibly because the high blood levels of estrogen promote a cytokine shift from a type 1 cytotoxic profile to an anti-inflammatory type 2 profile[187,169]. The reduced inflammatory activity may allow a reduction in the dose of prednisone or its elimination[169]. Exacerbations of disease activity are common after delivery (12%-86%), presumably because the falling blood concentrations of estrogen facilitate a cytokine shift back to the cytotoxic type 1 profile[163,164,169]. These flares must be anticipated, and conventional dosing with prednisone should be resumed during the third trimester (Table 4).

Women with autoimmune hepatitis should not be discouraged from pregnancy, but they must be counseled about the increased frequency of prematurity and fetal loss, the normal low occurrence of congenital defects, the theoretical hazards of azathioprine during pregnancy, the possibility of an exacerbation of the liver disease after delivery, the need for high-risk obstetrical care, and the reasons for regular medical assessment during and after the pregnancy[30].

CONCLUSION

Current corticosteroid regimens (Table 1) are effective in the management of most patients with autoimmune hepatitis, and new pharmacological agents with powerful site-specific actions promise to strengthen the therapeutic repertoire. These treatments must be adapted and integrated to satisfy individual clinical situations. Established therapies can be improved by defining end points that permit optimal opportunity for resolution without extending beyond achievable goals and introducing undue risk of drug toxicity. The ideal treatment end point is normalization of liver tests and liver tissue, and the expected duration of initial therapy to achieve this end point is ⩽ 24 mo (Table 2).

Autoimmune hepatitis is by nature an aggressive liver disease with fluctuating activity. Mild asymptomatic disease may be a temporary condition, and corticosteroid therapy should be considered for all patients regardless of disease activity at presentation. Other variations in the clinical phenotype, including acute severe (fulminant) presentations, absence of autoantibodies, and cholestatic features (overlap syndromes), warrant management appropriate for the predominant manifestations of the disease (Table 2).

Relapse after drug withdrawal justifies a long-term maintenance regimen with azathioprine, and azathioprine can also be used as a single-drug therapy for patients with an incomplete response to conventional schedules. Treatment adjustments are warranted in elderly patients who respond slowly and in pregnant patients in whom azathioprine avoidance is prudent and postpartum exacerbations are possible (Tables 3 and 4).

Empiric salvage therapy includes the calcineurin inhibitors (cyclosporine and tacrolimus) and mycophenolate mofetil, and they can be introduced judiciously for otherwise refractory inflammation (cyclosporine or tacrolimus) or drug intolerance (mycophenolate mofetil) (Table 4). Salvage therapy is expensive, unproven, associated with its own toxicity, inconsistently effective, and poorly guided. It should never supersede indications for liver transplantation.

Treatment decisions in autoimmune hepatitis will not be difficult if they are guided by an awareness of the phenotypic diversity of the disease, realistic therapeutic expectations, willingness to make individualized adjustments according to the clinical need, and familiarity with the alternative empirical therapies.

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