Review

Pathogenesis, Diagnosis, and Treatment of Alcoholic Liver Disease

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Alcohol-related liver disease is a major cause of morbidity and mortality in the United States. Alcoholic liver disease encompasses a clinicohistological spectrum, including fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. Fatty liver is a benign and reversible condition, but progression to alcoholic hepatitis and cirrhosis is life-threatening. Alcoholic hepatitis is diagnosed predominantly on clinical history, physical examination, and laboratory testing, although liver biopsy is often necessary to secure the diagnosis. The major focus of management is abstinence from alcohol, supportive care, treatment of complications of infection and portal hypertension, and maintenance of positive nitrogen balance through nutritional support. Corticosteroid therapy is controversial but should be considered in patients with a discriminant function greater than 32 and/or presence of spontaneous hepatic encephalopathy in the absence of infection, gastrointestinal bleeding, and renal failure. The only curative therapy for advanced alcoholic cirrhosis is liver transplantation. Several recent advances in understanding the pathogenesis of alcoholic liver disease may lead to novel future treatment approaches, including inhibition of tumor necrosis factor α, antioxidant therapy, stimulation of liver regeneration, and stimulation of collagen degradation.

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAGE = alcoholism screening tool containing 4 structured questions; DF = discriminant function; GI = gastrointestinal; MCV = mean corpuscular volume; NF-κB = nuclear factor κB; TNF = tumor necrosis factor

CLINICAL DIAGNOSIS

Clinical Spectrum

Alcoholic liver disease spans a clinical and histological spectrum, from fatty liver to alcoholic hepatitis to alcoholic cirrhosis. Fatty liver develops in most people who abuse alcohol for a period of days. However, this condition is generally asymptomatic and entirely reversible with abstinence. Although the majority of people who abuse alcohol for an extended duration do not develop advanced lesions of alcoholic liver disease, approximately 15% to 20% develop alcoholic hepatitis and/or cirrhosis, which may develop in succession or exist concomitantly. The level of alcohol consumption necessary for the development of these advanced forms of alcoholic liver disease is probably 80 g of alcohol per day, the equivalent to 6 to 8 drinks daily for several years.[1] Women have a significantly higher risk of developing alcoholic liver disease than do men for any given level of alcohol intake[2-4] (Table 1). Although various mechanisms have been proposed, decreased gastric metabolism of alcohol relating to decreased gastric alcohol dehydrogenase activity in women may have a role in the increased susceptibility of women to alcohol-related liver injury.[6] However, the threshold of alcohol necessary for the development of advanced alcoholic liver disease varies substantially among individuals, and factors other than absolute alcohol consumption clearly have an important role in determining who will develop alcoholic liver disease and who will not. These observations highlight the role of genetic factors that may predispose specific persons to greater propensity toward alcohol-induced liver toxicity. Specific genetic polymorphisms have been detected in patients with alcoholic liver disease, most notably mutations in the tumor necrosis factor (TNF) promoter and mutations in alcohol-metabolizing enzyme systems, including alcohol dehydrogenase, aldehyde dehydrogenase, and the microsomal ethanol oxidizing system.[7] Infection with hepatitis C virus also increases the severity of liver injury in patients with alcoholic liver disease,[8] and some studies suggest that obesity may be a risk factor.[9,10]

History and Examination

The major clinical assessment necessary for diagnosing alcoholic liver disease is determining whether the patient is abusing alcohol. However, this determination is not always straightforward. Alcoholic patients and even their family members often minimize or conceal alcohol use. Interrogation of multiple family members is often necessary to uncover the true level of alcohol consumption. Additionally, different caregivers often obtain disparate histories from the patient because of the relationship between the patient

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Table 1. **Relative Risk of Alcoholic Liver Disease at Different Levels of Alcohol Intake**

Weekly units* of alcohol intake	Alcoholic cirrhosis		Alcoholic liver disease	
	Men	Women	Men	Women
<1	3.7	1.09	1.8	1.0
1-6	1.0	1.0	1.0	1.0
7-13	0.9	4.1†	1.1	2.9†
14-27	1.6	3.1†	1.4	2.9†
28-41	7.0†	16.8†	3.8†	7.3†
42-69	13.0†	NR	5.9†	NR
≥70	18.1†	NR	9.1†	NR

*Unit represents 10 to 12 g of alcohol (12 oz of beer, 4 oz of wine, 1 oz of spirits).
†Represents a statistically significant increased relative risk of having alcoholic liver disease. NR = not reported.
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and caregiver, the level of trust, and the approach and persistence caregivers may use in obtaining the alcohol history. Questionnaires have been used to clarify alcohol use and abuse syndromes. Some of these, such as the Minnesota Multiphasic Personality Inventory substance abuse scale[11] and the Michigan Alcoholism Screening Test,[12] have been used predominantly for research purposes because of their length. A clinically useful test is the CAGE questionnaire[13]: Have you ever thought you should ***c***ut down on your drinking? Have people ***a***nnoyed you by criticizing your drinking? Have you ever felt bad or ***g***uilty about your drinking? Have you ever drunk alcohol the first thing in the morning to steady your nerves or to try to get over a hangover (***e***ye-opener)? Any positive responses to these inquiries require more detailed investigation and raise the possibility of alcohol abuse.

However, the CAGE questionnaire, like any history-gathering tool, is susceptible to patient deception. Because of the inherent difficulties in obtaining a reliable history of alcohol use, various biochemical markers have been evaluated for their ability to detect surreptitious alcohol abuse. Most of the traditional serologic markers of alcohol abuse are based on indirect assessment of alcohol abuse through evaluation of liver injury. These include elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, the elevated AST/ALT ratio, and the elevated γ-glutamyltransferase level. However, because these tests assess alcohol abuse indirectly via detection of liver injury, they have diminished sensitivity and specificity, generally less than 70%. The mean corpuscular volume (MCV) is also elevated with alcohol abuse because of the bone marrow toxicity of alcohol, although its sensitivity as a marker of alcohol use is generally lower than 50%.[14] Because of these inherent limitations in diagnostic accuracy, newer tests have been evaluated for their ability to detect alcohol abuse.[15] These include carbohydrate-deficient transferrin and mitochondrial AST as well as ratios utilizing these factors in conjunction with total transferrin and AST, respectively. Carbohydrate-deficient transferrin reflects the desialylation of transferrin, which occurs in response to high alcohol use and develops independent of liver injury.[16] The test value is elevated for weeks after heavy alcohol use and subsequently diminishes into the normal range. Carbohydrate-deficient transferrin may be specific for alcohol use; however, its lack of sensitivity precludes its routine use alone in the diagnosis of active alcoholism, although the test is used at some medical centers with additional complementary tests.[17,18] Mitochondrial AST is a specific isoform of the AST enzyme that is released from hepatocytes at particularly high levels in association with alcohol abuse.[15] Despite the initially promising results observed with both these tests, neither has consistently been shown to be of greater utility than the time-tested and economical measurements of AST/ALT, γ-glutamyltransferase, and MCV.

Alcoholic fatty liver is predominantly an asymptomatic condition that develops in response to a short duration (a few days) of alcohol abuse. Prolonged alcohol abuse results in alcoholic hepatitis. The history of patients with this condition is notable for various constitutional symptoms, such as fatigue, anorexia, and weight loss, and other nonspecific symptoms, such as nausea and vomiting. Severe alcoholic hepatitis may be evident by advanced symptoms relating to portal hypertension, including gastrointestinal (GI) bleeding, ascites, and hepatic encephalopathy. Elicitation of risk factors for concomitant or alternative forms of acute and chronic hepatitis, such as viral hepatitis, Wilson disease, and drug-induced hepatitis, is important. Physical examination of patients with alcoholic hepatitis is most notable for hepatomegaly. Other findings depend on the severity of liver insult and may include jaundice, splenomegaly, hepatic bruits, collateral vessels, and ascites. Alcoholic cirrhosis may occur before, concomitant with, after, or independent of a bout of alcoholic hepatitis. The clinical history is similar to that of alcoholic hepatitis, and symptoms are similar to those observed with other forms of end-stage liver disease. Additionally, poor nutritional status, peripheral neuropathy, dementia, or cardiomyopathy may coexist because of the extrahepatic toxicities of alcohol abuse.

Laboratory Values and Imaging Studies

Although specific laboratory abnormalities reflect the severity of alcohol-induced liver injury and have prognostic utility, others are useful only diagnostically. Transaminase levels are elevated less than 5 to 10 times the normal

value in the absence of concomitant acetaminophen abuse. Additionally, the AST level is almost always greater than the ALT level, and a reversal of this ratio suggests the presence of concomitant viral hepatitis or alternatively the presence of nonalcoholic steatohepatitis.[19] Both the modest level of increase and the predominance of the AST level help to distinguish alcoholic hepatitis from acute viral hepatitis. However, transaminase levels alone have no prognostic utility. In more moderate to severe alcoholic hepatitis, prothrombin time and bilirubin level are also elevated, and the presence of leukocytosis and right upper abdominal quadrant discomfort may mimic biliary tract disease. In contrast to the transaminase levels, the prothrombin time and bilirubin level reflect the severity of alcoholic hepatitis and are of prognostic importance. Several groups have attempted to use the bilirubin level and prothrombin time as well as other laboratory variables to assess prognosis of patients with alcoholic hepatitis. The simplest and most effective of these assessments is the Maddrey discriminant function (DF) analysis [DF = 4.6 (prothrombin time in seconds – control) + serum bilirubin (mg/dL)]. An increase in DF of more than 32 effectively identifies patients at a high risk of death, more than 50%. The Child-Pugh score and the Combined Clinical Laboratory Index have also been used effectively in this manner.[20,21] Doppler ultrasonography is often a useful adjunct to exclude alternative diagnoses, such as cholecystitis, biliary obstruction, and hepatic vein thrombosis, which may result in some overlapping clinical symptoms particularly in the absence of an accurate alcohol history. Additionally, the presence of fatty infiltration on imaging studies (ultrasonography and computed tomography) may provide further clues to the diagnosis of alcohol-related liver injury.

Liver Biopsy and Histology

Liver biopsy is generally unnecessary for diagnosing alcoholic fatty liver because the condition is benign and reversible. However, in some patients, biopsy may be performed to determine the degree of advancement of alcoholic liver disease and to exclude the presence of cirrhosis. With the advances in serologic and genetic diagnoses of infectious and metabolic hepatitides during the past decade, alcoholic hepatitis is often diagnosed on clinical and laboratory findings, although some diagnostic uncertainty may remain in the absence of histological confirmation.[22,23] Liver biopsy is often useful to secure the diagnosis and to determine the extent of liver injury, but this procedure is associated with risk in patients with coagulopathy and thrombocytopenia. Thus, the use of liver biopsy in such patients varies among experienced clinical hepatologists, and the risk-benefit ratio of the procedure must be individualized in the clinical setting depending on the required level of diagnostic certainty.[24] For example, biopsy is necessary when the diagnosis is questionable and specific therapy is contemplated.[25] Liver biopsy demonstrates several characteristic features of alcoholic hepatitis, including polymorphonuclear infiltrates, centrilobular hepatocyte swelling and degeneration, macrovesicular and microvesicular steatosis, Mallory bodies, and pericentral-perisinusoidal fibrosis (Figure 1). In 50% to 93% of patients who undergo biopsy, fully developed cirrhosis may be observed concomitant with alcoholic hepatitis.[26] In addition to confirming the diagnosis, biopsy aids in excluding other coexisting conditions, such as hepatitis C, hemochromatosis, or Wilson disease. Of importance, the biopsy findings in alcoholic hepatitis are remarkably similar to those observed in nonalcoholic steatohepatitis; however, for the same extent of histological abnormalities, patients with alcoholic hepatitis tend to be clinically more ill than those with nonalcoholic steatohepatitis.

MANAGEMENT AND TREATMENT ISSUES

Management issues depend on the extent of alcoholic liver injury. Isolated fatty liver requires no management other than abstinence. For alcoholic hepatitis, a myriad of treatment options have been evaluated over the years; however, current therapy still focuses predominantly on supportive care.[26] Curative treatment of decompensated alcoholic cirrhosis is limited to liver transplantation in a select subgroup of patients.

Abstinence From Alcohol and Treatment of Addiction

The most important factor in both short-term and long-term survival of patients with alcoholic liver disease is abstinence from alcohol. Patients who recover from alcoholic hepatitis and maintain abstinence may evidence continuing improvement in clinical sequelae and laboratory variables for as long as 6 months. Continued alcohol use is detrimental, with a 7-year survival rate of 50% in those who continue to drink alcohol compared with an 80% survival rate in those who discontinue alcohol intake.[27] However, survival is also adversely influenced by concomitant presence of cirrhosis and its ensuing complications.[28] Treatment of addiction requires a multidisciplinary approach, including an addiction specialist, primary care physician, and psychiatrist.

Nutrition

Patients with progressive alcoholic liver disease are invariably malnourished because of various factors, including poor diet, anorexia, and encephalopathy. Maintenance of positive nitrogen balance and provision of adequate energy requirements through nutritional support are vital.

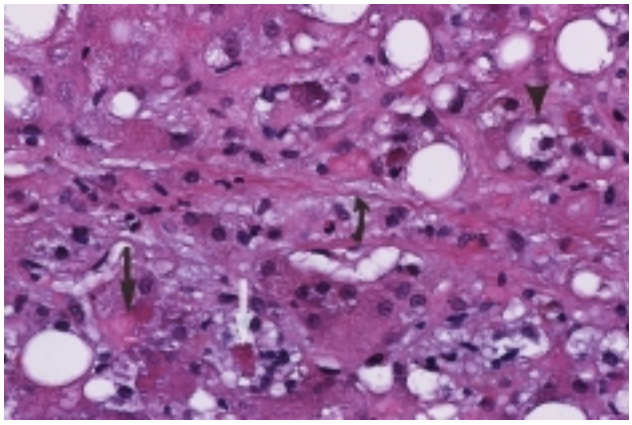

Figure 1. Photomicrograph of liver biopsy specimen showing steatosis with irregular hepatocyte swelling (arrowhead), apoptosis (white arrow), Mallory hyaline (large arrow), and pericellular fibrosis (curved arrow) (hematoxylin-eosin, original magnification ×40).

Additionally, protein and energy needs are generally increased in patients with alcoholic hepatitis because of stress of illness and underlying malnutrition. However, provision of nutrients in excess of calculated requirements is unlikely to be of additional benefit. Enteral provision of adequate calories is optimal. However, in patients with severe disease, anorexia and encephalopathy may precipitate the need for parenteral supplements. Additionally, parenteral nutritional support may be necessary in patients with ileus and coma, although the survival benefit of parenteral nutritional supplementation in such patients is not established because of iatrogenic complications that can arise concomitant with parenteral access, most notably a propensity for nosocomial infection. Generally, encephalopathy should not be a cause for protein restriction, and most patients can tolerate a 60-g protein diet. In patients in whom severe encephalopathy is exacerbated by dietary protein, branched chain amino acid supplements or vegetable protein substitution should be considered. Some studies suggest that androgenic anabolic steroids such as oxandrolone may be of use in malnourished patients; however, more studies are needed to confirm this approach.[27]

Portal Hypertension

Patients with alcoholic cirrhosis and those with isolated alcoholic hepatitis may develop complications of portal hypertension. The clinical observation of portal hypertension in the absence of cirrhosis is supported by studies showing that alcohol directly increases portal pressure and highlights the vascular component of intrahepatic resistance and portal hypertension.[29] Common portal hypertensive complications that require therapy include hepatic encephalopathy, bleeding esophageal varices, ascites and spontaneous bacterial peritonitis, and hepatorenal syndrome, all of which portend severe disease and a poor prognosis.

Infection

Infection is one of the most common causes of death in patients with alcoholic hepatitis. Malnutrition, underlying liver cirrhosis, and aggressive in-hospital medical procedures all contribute to the risk of infection. Additionally, alcohol-induced gut permeability to microbes probably contributes to this risk. Because of their relative degree of immunocompromise, patients with alcoholic hepatitis must be evaluated carefully for infections and treated aggressively. Particularly frequent infectious insults include spontaneous bacterial peritonitis, aspiration pneumonia, and lower extremity cellulitis.

Liver Transplantation

Alcoholic liver disease is currently the second most common indication for liver transplantation in the United States. Despite popular opinion, patients who undergo transplantation because of alcoholic liver disease have excellent survival rates posttransplantation, superceded only by survival rates observed in patients who undergo transplantation because of chronic cholestatic liver disease.[30] A major issue in maintaining excellent outcomes in this patient population is identifying candidates with a low risk of recidivism after transplantation because alcohol abuse after liver transplantation can result in rapid development of cirrhosis in the graft, interfere in the compliance and bioavailability of immunosuppressive medications, and alter the perceptions of the general public and potential organ donors in a detrimental way.[31] Most studies suggest that alcohol relapse after transplantation occurs in 15% to 30% of patients.[32] Although this figure may be low because many patients do not admit to relapse, the low incidence of observed graft injury and loss due to recurrent alcoholic liver disease suggest that most of these patients do not drink alcohol to an extent that is detrimental to their graft and health. Selection of appropriate patients for liver transplantation requires a team approach, including a hepatologist, surgeon, addiction specialist, psychiatrist, and social worker. At present, most transplant centers require patients to have 6 months of abstinence and appropriate addiction treatment before they can undergo liver transplantation. Patients with active alcoholic hepatitis are not candidates for liver transplantation because of their lack of demonstrated abstinence and high perioperative mortality. Interestingly, the decision-making process regarding transplantation for most alcoholic patients with end-stage liver disease is not done at the transplant center but is determined by their primary referring physician because most patients with alcoholic cirrhosis are not referred for transplantation.[32]

Corticosteroids

Alcoholic hepatitis is an inflammatory form of liver injury. Additionally, the high incidence of autoimmune markers in patients with alcoholic hepatitis suggests an autoimmune component to the pathogenesis of injury. Corticosteroids possess potent anti-inflammatory qualities and are useful for treating autoimmune hepatitis. Based on this rationale, investigators have examined the role of corticosteroids in the treatment of alcoholic hepatitis. However, after completion of more than 12 randomized controlled clinical trials and meta-analyses[33,34] on this topic, consensus is lacking regarding the use of corticosteroids in patients with alcoholic hepatitis. Most of the early trials[35-38] of corticosteroids did not show a statistically significant survival benefit in patients with alcoholic hepatitis except for 2 studies[39,40] performed at the University of North Carolina. However, subgroup analysis of the initial studies suggested that patients with hepatic encephalopathy might benefit from corticosteroid therapy.[41]

Discriminant analysis of factors associated with survival indicated that patients with increased bilirubin levels and prothrombin times might benefit from corticosteroids. Therefore, follow-up studies focused on the role of corticosteroids in the treatment of patients with a DF greater than 32 and/or the presence of spontaneous hepatic encephalopathy. Some patients may be too ill to benefit from corticosteroids, and thus those with renal failure, infection, or GI bleeding were excluded from many of these trials. Although several similarly designed, well-conducted studies showed that corticosteroids reduced mortality in patients with alcoholic hepatitis who had a DF greater than 32 and/or spontaneous hepatic encephalopathy, conferring benefit up to 1 year from treatment,[42-44] a large study[45] failed to show a survival benefit of corticosteroids in patients with moderate and severe alcoholic hepatitis. Thus, the efficacy of corticosteroids is controversial. Because of the disparity in treatment outcomes among trials, some investigators performed meta-analyses to evaluate the effects of corticosteroids on survival in patients with alcoholic hepatitis. The 2 major peer-reviewed meta-analyses were by Imperiale and McCullough[33] and Christensen and Gluud.[34] Both studies clearly showed that corticosteroids are unlikely to be of benefit in patients without hepatic encephalopathy. In patients with encephalopathy, 1 meta-analysis[33] concluded that there was a modest survival benefit in the absence of GI bleeding, but the other[34] did not support this conclusion. Clearly, most patients with alcoholic hepatitis are *not* candidates for corticosteroids, including those with a DF lower than 32 and no hepatic encephalopathy, as well as those with GI bleeding, renal failure, or infection. However, corticosteroids should be considered in patients with a DF greater than 32 and/or spontaneous hepatic encephalopathy in the absence of infection, GI bleeding, and renal failure based on the positive results of some of the aforementioned studies. Nonetheless, the survival benefit in this select population is modest, about 25% to 33%, with a mortality rate of almost 50%. Additionally, this select group of patients constitutes a minority of patients with alcoholic hepatitis, highlighting the need for alternative therapies.

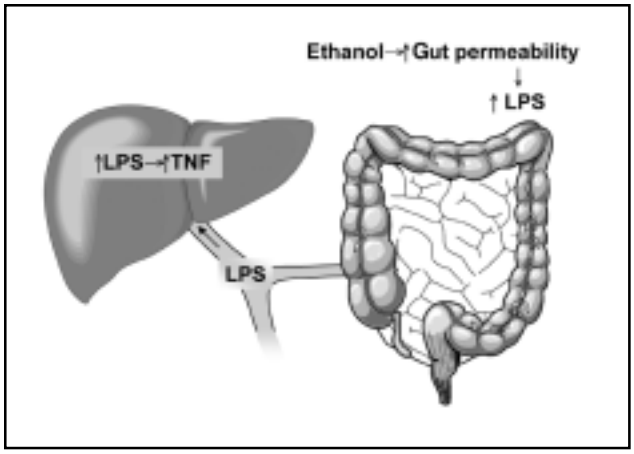

Figure 2. Alcohol-induced tumor necrosis factor (TNF) production. Ethanol increases gut permeability, allowing lipopolysaccharide (LPS) from enteric bacteria to travel to the liver via the portal vein. In the liver, LPS stimulates Kupffer cells to produce TNF.

PATHOGENIC MECHANISMS AND NOVEL TREATMENT APPROACHES

Because of the lack of effective therapies and high mortality rate of patients with alcoholic hepatitis and alcoholic cirrhosis, novel treatment options are being investigated. Many potential treatments are based on modulation of putative pathogenic mechanisms thought to be involved in the development of alcoholic liver disease.

Tumor Necrosis Factor

Experimental evidence suggests that cytokine pathways signaling cell death are critical in initiating and/or perpetuating alcohol-induced liver injury through apoptosis and necrosis.[46-48] In particular, apoptosis appears to be a prominent event in both clinical and experimental alcoholic liver disease.[49] The initial event may be mediated by the effects of alcohol on the gut. For example, alcoholic patients with chronic liver disease have a significant increase in intestinal permeability, which facilitates the uptake of gut-derived endotoxin into the portal circulation (Figure 2). In the liver, endotoxin is phagocytosed predominantly by Kupffer cells where endotoxin stimulates the release of TNF-α.

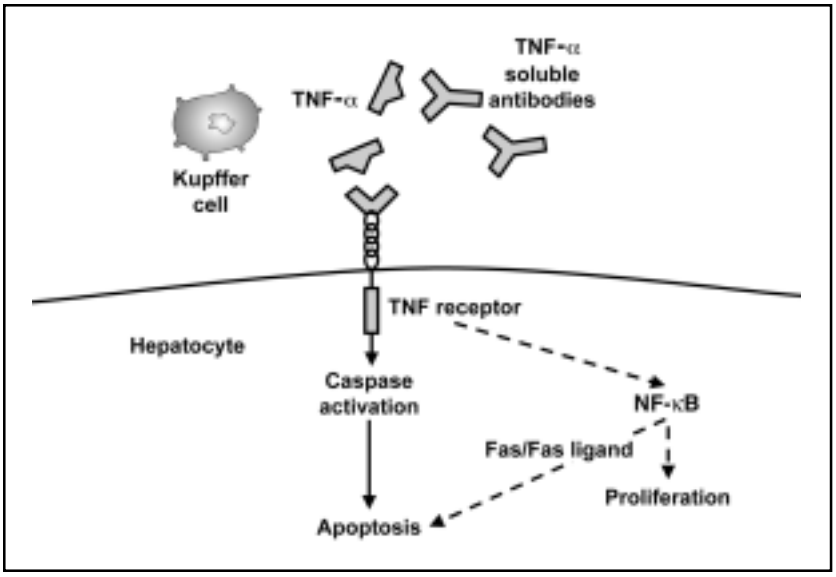

Figure 3. Tumor necrosis factor (TNF) signals lead to hepatocyte apoptosis. TNF derived from Kupffer cells binds to receptors on hepatocytes. TNF binding to its receptor can be inhibited through soluble antibodies. Binding initiates cell signals that culminate in apoptosis or cell death predominantly through activation of intracellular caspases or alternatively activates the nuclear factor κB (NF-κB) pathway, which may result in proliferative or apoptotic events.

Tumor necrosis factor-α was first identified in 1975 as a macrophage-derived factor that caused cell necrosis and cachexia. Transcription of the *TNF* gene results in secretion of an inactive 17-kd protein that subsequently trimerizes to form a 51-kd active form of TNF-α ligand.[50] Two distinct TNF receptors have been identified on most cell types, a 55-kd and a 75-kd receptor.[50] Circulating TNF trimers bind to these TNF-α receptors, particularly the 55-kd receptor, resulting in cross-linking and signal transduction.[50] Stimulation of the 55-kd receptor by TNF-α activates 2 signaling cascades: (1) a cell death cascade and (2) a pathway mediated by the nuclear factor κB (NF-κB) (Figure 3). The NF-κB pathway is thought to inhibit cell death and prevent cytotoxicity. Why hepatocytes in patients with alcoholic liver disease become susceptible to TNF despite NF-κB activation is unclear. Depletion of mitochondrial antioxidants, such as glutathione, during alcohol exposure has been proposed as a mechanism to explain TNF cytotoxicity in this disease.[51] An alternative explanation is the generation of cytotoxic factors by NF-κB in the presence of alcohol. Indeed, an increase in the expression of apoptosis markers, including the death receptor Fas and its ligand, has been detected in patients with alcoholic hepatitis.[52-54]

Several lines of clinical experimental evidence in patients suggest that TNF may have a critical role in the pathogenesis of liver injury associated with alcoholic hepatitis. In support of this concept, the biological actions of TNF-α include fever, neutrophilia, and hypotension, clinical features that are also seen in patients with acute alcoholic hepatitis.[55] Additionally, investigators have shown that plasma levels of TNF-α are increased in patients with alcoholic hepatitis and may correlate with mortality.[56,57] Furthermore, TNF-α production by peripheral blood monocytes and Kupffer cells in patients with alcoholic hepatitis is increased, suggesting that such patients may have a lower threshold for TNF release in the presence of endotoxin.[58]

Based on the hypothesis that TNF-α has an important role in toxin-mediated hepatic injury,[48] investigators have studied the role of antibodies to TNF-α in suppressing liver injury caused by chronic exposure to alcohol in experimental animal models. Iimuro et al[59] showed that a single infusion of anti–TNF-α antibody was sufficient to attenuate the necrosis and inflammation caused by chronic exposure to alcohol in the rat. These multiple lines of clinical and experimental evidence raise the possibility that inhibition of TNF, its downstream signals, or Fas could attenuate alcoholic liver disease in humans. Indeed, a recent report suggested that pentoxifylline, a pharmacological inhibitor of TNF release, may be of benefit in patients with alcoholic hepatitis.[60] Based on these experimental observations, studies using commercially available human anti-TNF antibodies may be warranted.

The role of TNF in mediating liver steatosis and inflammation remains controversial, and TNF by itself is unlikely to be sufficient to produce alcoholic liver injury.[61] Other proinflammatory cytokines also have a role in the pathogenesis and/or symptoms of acute alcohol-related liver injury. For example, both interleukin 6 and interleukin 8 levels are elevated in patients with alcoholic liver disease and correlate with features of disease severity.[62] Additionally, other mechanisms of alcohol-induced liver injury are important, including the role of oxidative stress, lipid peroxidation, and acetaldehyde, as described subsequently.

Oxidative Stress and Hepatocyte Membrane Injury

Alcohol-induced liver injury occurs in part through oxidative stress with key oxidants derived from NADPH oxidase and/or cytochrome P-450 2E1.[63,64] Moreover, antioxidants, including *S*-adenosyl-*L*-methionine and glutathione, are reduced, further exacerbating the imbalance between oxidants and antioxidants.[65] Oxidative stress, in conjunction with acetaldehyde-protein adduct formation and lipid peroxidation, may contribute to the alterations in membrane function and ensuing hepatocyte injury characteristic of alcoholic liver disease.[66] To reduce hepatic oxygen consumption, investigators have examined the role of propylthiouracil in patients with alcoholic hepatitis. Although a randomized controlled trial showed clinical benefit, follow-up studies have been inconclusive.[67,68] Additionally, because of the inherent hepatotoxicity of propylthiouracil, this drug remains experimental. Investigators have examined the effects of other antioxidant compounds. Although silymarin recently was shown to be of no benefit in patients with alcoholic hepatitis, evaluation of *S*-adenosyl-*L*-methionine showed a modest beneficial effect.[69,70]

Liver Regeneration

Alcoholic hepatitis is characterized by death and injury of hepatocytes. Therefore, therapies to stimulate proliferation of hepatocyte mass are rational.[71] This concept has been examined in patients with alcoholic hepatitis by treatment with insulin and glucagon, which is thought to stimulate liver regeneration. However, the results have been discouraging, and cases of severe hypoglycemia have dimmed enthusiasm for this approach.[26] Therapies using more selective hepatotropic agents, such as hepatocyte growth factor, are compelling but remain untested because of the tumorigenic potential of this growth factor.

Collagen Degradation

The development of pericentral fibrosis portends irreversible architectural changes in patients with alcoholic hepatitis. The alcohol metabolite acetaldehyde may have an important role in the development of alcohol-induced fibrosis because of stimulation of collagen deposition by hepatic stellate cells.[72] Therefore, novel therapies to inhibit and reverse collagen deposition remain the ultimate goal for hepatologists who study and treat liver cirrhosis. Colchicine has been evaluated in patients with alcoholic liver disease. This agent inhibits collagen deposition, and an initial trial suggested benefit in patients with alcoholic liver cirrhosis.[73] However, studies in patients with alcoholic hepatitis have shown no clinical benefit.[74] Trials are now under way in humans to examine the effects of phosphatidylcholine, an agent effective in reducing liver fibrosis in alcohol-fed baboons, which is thought to be beneficial in part through antifibrotic actions.

Photomicrograph courtesy of Dr Lawrence J. Burgart, Mayo Clinic, Rochester, Minn.

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