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Alcoholic Liver Disease: A Synopsis of the Charles Lieber's Memorial Symposia 2009–2012

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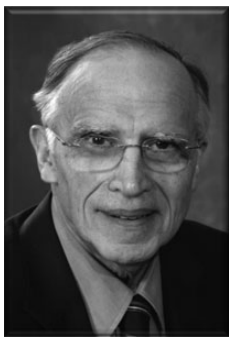
Abstract — This paper is based upon the 'Charles Lieber Satellite Symposia' organized by Manuela G. Neuman at each of the 2009–2012 Research Society on Alcoholism (RSA) Annual Meetings. The presentations represent a broad spectrum dealing with alcoholic liver disease (ALD). In addition, a literature search (2008–2013) in the discussed area was performed in order to obtain updated data. The presentations are focused on genetic polymorphisms of ethanol metabolizing enzymes and the role of cytochrome P4502E1 (CYP2E1) in ALD. In addition, alcohol-mediated hepatocarcinogenesis, immune response to alcohol and fibrogenesis in alcoholic hepatitis as well as its co-morbidities with chronic viral hepatitis infections in the presence or absence of human deficiency virus are discussed. Finally, emphasis was led on alcohol and drug interactions as well as liver transplantation for end-stage ALD.



Charles Saul Lieber, 1931–2009

INTRODUCTION

Charles S. Lieber was a pioneer of modern research on alcohol and alcohol-induced liver damage. Still in the 1950s it was believed that alcoholic cirrhosis is primarily due to malnutrition and not to the toxic effect of ethanol itself. Indeed, the cirrhosis of the alcoholic patient was called nutritional cirrhosis. With time strong epidemiological and experimental evidence has led to the recognition of the key toxic role of alcohol in the pathogenesis of alcoholic liver disease (ALD). It is the merit of Charles Lieber that ethanol by itself was identified as a hepatotoxin. Clinical and experimental inconsistencies with a view that alcoholism leads to cirrhosis only as a result of the associated malnutrition led to a series of experimental studies which have clearly demonstrated that alcohol is a hepatotoxin and that the toxicity of alcohol plays a major role in the etiology of cirrhosis in alcoholics.

One of Dr Lieber's most important discoveries was the description of a new pathway for alcohol metabolism: the cytochrome P450 2E1 (CYP2E1) dependent microsomal ethanol oxidizing system (MEOS). The elucidation of this pathway has contributed to the identification of many mechanisms responsible for alcohol-drug interaction, alcohol-mediated carcinogenesis, alcohol-associated changes in the intermediary metabolism and alcohol-related organ damage. The pathological consequences of chronic alcohol abuse are multifactorial and multisystemic. Although, some questions in the pathogenesis of ALD remain still. It has been shown that a variety of factors acting in concert are responsible for the toxic action of alcohol. Therefore, the amount of alcohol consumed, the pattern of drinking, genetics, gender, age, the presence of other types of liver disease, interactions with drugs and xenobiotics, the use of vitamin A may modulate ALD.

Alcohol consumption is still a major health problem in many countries. Though alcohol consumption in Europe decreased in the 1999, it increased in a high level between 2004 and 2006 with variation among the countries. Binge-drinking especially at young age became the major health problem in Europe and also in several countries alcoholism contributes to morbidity and mortality. The present review focuses in several aspects related to alcohol toxicity in humans and shows how many aspects of ALD initiated and discovered by Charles Lieber has been extended and clarified by others in the last decades.

ALCOHOL METABOLISM AND ALCOHOLIC LIVER DISEASES

Samir Zakhari, Radu M. Nanau, Manuela G. Neuman

The alcohol dehydrogenase pathway and mitochondrial injury

The major alcohol metabolic pathway in the liver involves the oxidative metabolism via the cytosolic enzyme alcohol dehydrogenase (ADH) (Lieber *et al.*, 1994). ADH metabolizes alcohol to acetaldehyde, a highly toxic molecule. Acetaldehyde is further metabolized by mitochondrial aldehyde dehydrogenase (ALDH) (Josan *et al.*, 2013). Alcohol oxidation results in reduction of the coenzyme nicotinamide-adenine-dinucleotide (NAD^+ to NADH). Mitochondrial NADH is then oxidized to the electronic transport chain. Acetaldehyde binds to macromolecules including nucleic acids, lipids and proteins leading to autoimmunity (Klassen *et al.*, 1995).

Since both NADH metabolism and acetaldehyde metabolism take place in the mitochondria, it is not surprising that excessive alcohol consumption leads to deficient mitochondrial nicotinamide-adenine-dinucleotide content, morphological changes in the mitochondria and alcoholic steatosis. Mitochondrial abnormalities have been described (Zimmerman, 1968) including distortion of shape and disorientation of cristae (Neuman *et al.*, 1999a,b) as well as the occurrence of megamitochondria (Horvath *et al.*, 1973). Mitochondrial dysfunction can contribute to the development of fatty liver (Feinman and Lieber, 1999). Mitochondria utilize and break down fatty acids as part of cellular respiration. The link between obesity, physical inactivity, alcohol consumption and type 2 diabetes is well established. Steatosis is considered as a risk factor that contributes to ALD and its degree of steatosis shows a good correlation with the severity of liver damage (McCullough and Falck-Ytter, 1999).

The cytochrome P402E1-dependent microsomal pathway and morphologic changes

In addition to the classical ADH pathway, a second pathway known as the microsomal ethanol oxidizing system (MEOS) also participates in alcohol metabolism, and is catalyzed by CYP2E1 (Lieber and DeCarli, 1968, 1970). This pathway has an enormous importance not only with respect to alcohol metabolism but also with respect to the toxic side effect associated with CYP2E1 induction (Lieber, 2004). CYP2E1 is located in the microsomes as well in the mitochondria (Bansal *et al.*, 2010). The ultrastructural proliferation of the smooth endoplasmic reticulum after alcohol consumption was the morphological adaptation to chronic alcohol consumption parallel by the functional adaptation of CYP2E1 induction. Other morphological features of ALD are the alcoholic hyaline or Mallory Denk bodies (Mallory, 1911; Biava, 1964; Porta *et al.*, 1965; Zimmerman, 1968; Yokoo *et al.*, 1972; Denk *et al.*, 1981; French, 1981; Cameron and Neuman, 1999). From a morphological perspective, early hepatocyte changes include accumulation of membrane-bound fat droplets, proliferation of the smooth endoplasmic reticulum and gradual distortion of mitochondria (Cameron and Neuman, 1999; Neuman *et al.*, 1999a,b). Lipid accumulation in ALD is largely macrovesicular and is comprised of neutral triglycerides. In addition, some histological findings such as perivenular fibrosis, and the presence of both microvesicular and macrovesicular fat, may be associated with an unfavorable prognosis in steatosis patients who have not yet developed cirrhosis (Worner and Lieber, 1985; Cameron and Neuman, 1999; Lefkowitch, 2005).

Genetic aspects of alcohol metabolism

Genetics and ethnicity play important roles in alcohol consumption and metabolism, as well as in the development of ALD, as indicated by family, twin, and adoption studies. Evidence suggesting genetic predisposition derives from the demonstration that the concordance of cirrhosis among monozygotic twins was more than twice that among dizygotic ones (Wilsnack *et al.*, 2009). A DH and ALDH provide important predisposition factors for alcohol-dependent sensitivity and more importantly ALD. Multiple forms of ADH are expressed by different organs. The liver expresses a majority of these forms which include class I (ADH1A, ADH1B and ADH1C), class II (ADH4), class III (ADH5), class IV (ADH7) and class V (ADH6) (Lai *et al.*, 2013; Zuo *et al.*, 2013). The frequency of class I ADH alleles varies in different populations. Thus, it is still an open question whether polymorphism in ADH1B and 1C plays a role in alcohol-associated disease.

The one significant genetic polymorphism in the ALDH2 gene results in the allelic variants ALDH2*1 and ALDH2*2. The latter of which is associated with a virtually inactive enzyme. Presence of the low activity ALDH2*2 allele defines a deficient phenotype, which is present in ~50% of Taiwanese, Han-Chinese and Japanese populations. On the other hand, a much lower frequency of this allele was found among Mongolian and Elunchun individuals in a Chinese population (Li *et al.*, 2012). Class I ADH and ALDH2 play a central role in alcohol metabolism. These genotypes modify the susceptibility of developing alcoholism and various types of tissue damage (Birley *et al.*, 2009). The activity of ADH and ALDH isozymes also contribute to alcohol-induced damage. Alcoholic cirrhosis is reduced by 70% in populations carrying the ALDH2*2 allele (Li *et al.*, 2012), while individuals with the ADH3*1 allele have an increased risk of developing breast cancer from moderate amounts of alcohol (Mao *et al.*, 2012). ALDH2*1, 2 heterocygots have also an increased risk of esophageal cancer.

In addition, CYP2E1 is also polymorphic with two alleles coding for protein with high and low activity, respectively (Oneta *et al.*, 2002; Stickel and Oesterreicher, 2006). Progression to ALD among heavy drinkers may be affected by the presence of the mutant CYP2E1 c2 allele (Grove *et al.*, 1998). Both heterozygosity for CYP2E1 c2 allele and homozygosity for ADH3*2 allele are independent risk factors for ALD in alcohol abusers (Lee *et al.*, 2001). Nevertheless, controversy surrounds these relationships (Lee *et al.*, 2001; Okamoto *et al.*, 2001; Vidal *et al.*, 2004). Zintzaras *et al.* (2006) further concluded in a meta-analysis of 50 association studies of ADH2, ADH3, CYP2E1 and ADLH2 polymorphisms that the information currently available is not enough to show a strong relationship and more rigorous studies are required.

Besides ethanol-mediated toxicity via ADH, ALDH and CYP2E1 metabolism resulting in acetaldehyde, NADH production and oxidative stress, elevated levels of lipopolysaccharides (LPS) have also been detected in blood of alcoholics (Bode *et al.*, 1987). It has been hypothesized that the increased levels of LPS contribute to the development of ALD by stimulating inflammatory cytokines. Alcoholics might develop tolerance to the chronic endotoxemia. In addition, increased translocation of endotoxin may have an important role (Bode and Bode, 2005).

CYP2E1 IN ALCOHOLIC LIVER DISEASE AND ALCOHOL-MEDIATED HEPATOCARCINOGENESIS

Sebastian Muller and Helmut Karl Seitz

Chronic alcohol consumption induces CYP2E1 by stabilizing it from degradation by the proteasome (French *et al.*, 2011). This increase in CYP2E1 has been reported not only in the liver but also in extrahepatic tissues such as the mucosal cells of the gastrointestinal tract (Seitz *et al.*, 1979, 1982) and in the

pancreas (Norton *et al.*, 1998). This induction may already occur with relatively low doses of chronic alcohol consumption such as 40 g/day and after 1 week and increases with time. However, it has to be emphasized that due to inter-individual variations not all subjects included in this study experienced the same magnitude of CYP2E1 induction (Oneta *et al.*, 2002).

CYP2E1 induction by chronic alcohol consumption results in a variety of complex cellular effects with enormous clinical significance. These include an increase in alcohol metabolism, increased production of reactive oxygen species (ROS) such as OH^- and H_2O_2, with increased cellular toxicity resulting in ALD and stimulating carcinogenesis (Seitz and Stickel, 2007), and interactions with various drugs, xenobiotics and carcinogens (Neuman *et al.*, 1999a; Seitz and Stickel, 2007; Whitcomb and Block 1994; Zimmerman 1981), increased degradation of retinol and retinoic acid and the generation of alcohol-induced fatty liver (Liu *et al.*, 2002). CYP2E1-induced oxidative stress also mediates the interaction between alcohol and other molecules such as xenobiotics, procarcinogens and retinoids (Seitz and Stickel, 2007).

ROS can directly damage proteins and *deoxy-ribo-nucleic acid* (DNA). Alternatively, ROS can bind to proteins, generating neoantigens that lead to an antibody response that may influence ALD. However, most important is the effect of ROS on lipid peroxidation leading to the formation of products such as 4-hydroxynonenal (4-HNE) and malondialdehyde. 4-HNE by itself may also bind to DNA nucleotides such as cytosine and adenosine, resulting in the generation of highly mutagenic and carcinogenic exocyclic etheno-DNA adducts (Moriya *et al.*, 1994; Nair *et al.*, 2010). CYP2E1 induction correlates well with the degree of hepatic fat, inflammation and fibrosis in a recent study of 90 patients with various degrees of ALD. Moreover, chronic alcohol consumption leads to an increase in CYP2E1 levels in the liver and in the human esophagus (Millonig *et al.*, 2011). CYP2E1 is induced in esophageal mucosa of chronic alcoholics and this induction correlates with the amount of alcohol consumed over the lifetime. This is in contrast to the liver where no correlation between the amount of alcohol intake and CYP2E1 induction is found. Furthermore, in esophageal biopsies of these patients, CYP2E1 induction correlates significantly with 4-HNE and also with exocyclic etheno-DNA adducts. This could be one mechanism by which alcohol induces cancer in the upper aerodigestive tract, especially in the esophagus (Millonig *et al.*, 2011).

In a carcinogenesis experiment with Sprague-Dawley rats, alcohol was administered chronically for 10 months after a single application of a small dose of the carcinogen diethylnitrosamine (20 mg/kg body weight) with or without chlormethiazole. CYP2E1 induction, associated with increased cellular proliferation rate, increases levels of nuclear factor-κB (NF-κB). 65 nuclear protein and glutathione-S-transferase, as well as positive foci presenting as precancerous lesions, are found after 1 month of feeding (Chavez *et al.*, 2011). In addition, four out of five animals developed liver adenomas after 10 months of feeding. When chlormethiazole is given adenoma production is completely prevented (Chavez *et al.*, 2011). This again shows that CYP2E1 is an important factor in hepatocarcinogenesis since its inhibition by chlormethiazole prevents hepatocarcinogenesis and normalization of retinoids (Liu *et al.*, 2002).

ALCOHOLIC LIVER DISEASE IN THE PRESENCE OF CHRONIC VIRAL HEPATITIS C INFECTION

Manuela G. Neuman

Viral hepatitis C (HCV) and viral hepatitis B (HBV) infection, as well as their co-morbidity with alcohol abuse are the foremost causes of chronic liver disease globally. Co-factors influencing HCV disease outcomes include age, gender and alcohol consumption, as well as immunologic and genetic factors. Hepatic oxidative stress results among others in overproduction of pro-inflammatory cytokines which in turn cause cellular stress and contributes to the development and progression of ALD (Neuman, 2003; Ambade and Mandrekar, 2012). Cytokines and chemokines are among the most prevalent factors known to contribute to alcoholic tissue injury, particularly in the liver (Neuman *et al.*, 1998). Endotoxin may induce TNF-α expression in liver cells, thereby producing additional inflammation. TNF-α is highly elevated in chronic and acute ALD (Neuman *et al.*, 2012a). In a recent study, Nguyen-Khac *et al.* (2010) shows no genetic differences in TNF-α receptors between alcoholic hepatitis (AH) patients and controls and thus, it appears that increased TNF-α secretion is a direct consequence of alcohol consumption in AH. A study of Machado *et al.* (2009) showed in 104 ALD that the simultaneous TNFR2 and TNF promoter gene polymorphism represent a higher risk for ALD. The selective up-regulation of chemokines by alcohol has been implicated in the pathogenesis of ALD (Neuman, 1999). Chemokines are a group of chemoattractant cytokines that enable cell migration. They have biological activity, regulating several conditions such as liver inflammation, liver fibrosis and angiogenesis (Neuman, 1999). Neuman *et al.* (2012a) reported increased IL-8 levels in patients with ALD, HCV and ALD/HCV when the histology activity index was high ($r = 0.96$) but normal IL-8 levels when the histology activity index was low. IL-8 was shown to correlate with a number of infiltrated tissue neutrophils in AH (Sheron *et al.*, 1993). The plasma IL-8 levels correlated with the severity of hepatic injury (Neuman *et al.*, 2012a). Moreover, IL-8 has been identified immunohistochemically in the liver in alcoholic patients (Neuman *et al.*, 2012a). Similarly, MCP-1 correlates with the number of monocytes and macrophages infiltrating the portal tract (Marra *et al.*, 1998). ALD patients had a high plasma MCP-1 level (Degré *et al.*, 2012). Moreover, the associations between MCP-1 and liver disease severity, as well as histological lesions, were correlated with neutrophil infiltration and IL-8 expression (Degré *et al.*, 2012).

Hepatic steatosis precedes the development of fibrosis in a variety of liver diseases, including HCV, ALD and non-alcoholic fatty liver disease (NAFLD) (McCullough and Falck-Ytter, 1999; Neuman *et al.*, 2008). A strong relationship among steatosis, diabetes, insulin resistance, higher body mass index, alcohol abuse, male gender and older age was found in a large meta-analysis of HCV patients, while progression of fibrosis appears to be mediated by inflammation (Leandro *et al.*, 2006). High levels of pro-fibrinogenic cytokines such as TGF-β and MMPs mediate fibrinogenesis in HCV and ALD patients (Neuman *et al.*, 2001, 2002a,b; Murphy *et al.*, 2002). Regardless of whether the hepatic insult is alcohol or viral hepatitis, repetitive or continuous injury to liver cells leads to the activation of inflammatory responses.

Hepatic stellate cells change from a quiescent to an activated phenotype. This activation process includes a phenotypic change to a myofibroblast-like cell, with increased proliferation rate, loss of retinoid stores, and increased production of ECM proteins (Neuman *et al.*, 1993; Lindquist *et al.*, 2000; Gäbele *et al.*, 2003). Hepatic stellate cells are the major source of ECM proteins in hepatic fibrosis, including type I collagen. In turn, myofibroblasts produce excessive amounts of collagens and ECM proteins and down-regulate MMPs. Also, ECM and the chemokines CXCR1 and CXCR2 augment the expression of TIMP-1 and TIMP-2. Enhanced TIMP-1 production can further advance proliferation and inhibit apoptosis of myofibroblasts, leading to continued ECM production and progressive fibrosis. Progression from fibrosis to cirrhosis is promoted by the combined effects of HCV infection, alcohol (toxic metabolites, LPS) and internal factors (genetic predisposition) (Neuman, 2003). Progressive fibrosis of the hepatic parenchyma leads to cirrhosis, nodule formation and altered hepatic function, increasing the risk of liver-related morbidity and mortality. There is little evidence that viral factors including viral load, viral genotype and quasispecies diversity significantly affect the risk of progression of liver disease in patients with ALD (O'Shea, *et al.*, 2010). Instead, host factors correlate with fibrosis progression, including older age at time of infection and male gender, as well as co-infection with HIV or with HCV (Macías *et al.*, 2012). Alcohol is the main factor associated with the progression of chronic AH to cirrhosis. Additional factors such as hepatic steatosis, schistosomal co-infection, iron overload, potentially hepatotoxic medications and environmental contaminants may also have important effects (Tsutsumi *et al.*, 1996; O'Shea *et al.*, 2010; Mathurin *et al.*, 2012).

Neuman *et al.* (2012a) assessed inflammation and fibrosis in a multinational study comprising Caucasian patients with ALD, HCV or ALD/HCV co-morbidity. Liver histology in individuals with dual pathology (i.e. ALD/HCV co-morbidity) differs among patients due to each individual's lifestyle. The major factors associated with fibrosis progression are older age at HCV infection and male gender (Neuman *et al.*, 2012a). In addition, serum levels of certain biomarkers were assessed in relation to inflammation and fibrosis in biopsies of patients with ALD, HCV or ALD/HCV co-morbidity. TNF-α levels increased significantly with increasing severity of inflammation. On the other hand, TGF-β and MMP2 levels increased significantly with increasing degree of fibrosis, as described by biopsy, regardless of the diagnosed disease. TGF-β levels were significantly higher in ALD patients compared with HCV patients. Long-established steatosis of grades 3–4 was associated with a higher rate of fibrosis progression (Neuman *et al.*, 2012a). Fibrosis progression in chronic hepatitis patients, including alcohol-induced hepatitis and chronic HCV, determines the ultimate prognosis. Monitoring of TGF-β and MMPs provides important insights into fibrosis. Furthermore, histological findings of hepatic fibrosis and total hepatic activity index score showed a significant correlation with serum albumin and platelet count in HCV-infected alcoholics. Correlation analysis also indicated that hyaluronic acid; serum albumin and platelet counts are the best predictors of the severity of liver damage at histology (Neuman *et al.*, 2012a). In patients with co-morbidity of ALD and HCV, TNF-α also acts as an important immunomediator. Alcohol induces pro-inflammatory cytokines that contribute to the enhancement of the liver damage promoted by HCV (Neuman *et al.*, 2012b).

ALCOHOL LIVER DISEASE AND HIV CO-MORBIDITY

Manuela G. Neuman, Radu M. Nanau, Michelle Schneider, Charles Parry, Romina Isip

Human immunodeficiency virus (HIV) infection and HCV-HIV co-infection can thus play an important role in alcoholic patients (Neuman *et al.*, 2012a). A clear connection between alcohol consumptions and HIV disease progression was established, especially among individuals receiving highly active antiretroviral therapy (HAART) (Samet *et al.*, 2003). Alcohol also poses an important medication management issue with significant implications with regards to the effectiveness of HAART in HIV patients, particularly through modification of liver drug metabolism. A connection between the adverse drug reactions (ADR) of ART and the toxic effects of alcohol is possible due to the similar types of injury associated with the two classes of drugs. In a recent systematic review analyzing HIV patients, current alcohol use disorders have been reported in 8–50% of individuals, with a lifetime prevalence of 26–60%. However, authors record sporadic reporting of alcohol use patterns (Neuman *et al.*, 2012b). A dose–response relationship between alcohol consumption and HAART non-adherence was shown, with drinkers missing more medication doses than non-drinkers (Braithwaite *et al.*, 2005). Alcohol abuse was associated with taking medication off schedule, as well as missing doses, nonrenewal of medications prescriptions and active substance misuse (Kalichman *et al.*, 2012; Neuman *et al.*, 2012b). Alcohol has a substantial influence on immunologic, virologic and pathologic disease characteristics in HIV monoinfected individuals and HIV/HCV co-infected patients (Benhamou *et al.*, 1999). Alcohol abuse is also often associated with numerous facets of HIV disease progression, ranging from immune system impairment to hepatotoxicity (Neuman *et al.*, 2012b). As an immunosuppressant, alcohol accelerates HIV disease progression through direct T cell apoptosis, mitochondrial damage, and inhibition of T cell responses, natural killer cell activity and macrophage phagocytic activity (Neuman *et al.*, 2012b). The increase in serum HCV RNA in habitual drinkers may be involved in the progression of liver disease (O'Shea *et al.*, 2010).

HIV positivity and excessive drinking are associated with cirrhosis although it appears that alcohol abuse is the primary determinant (Castellares *et al.*, 2008). Among these patients, co-infection with viral hepatitis is a significant risk factor for the development of cirrhosis (Castellares *et al.*, 2008). In addition, alcohol-induced cirrhosis can result in changes in drug metabolism in the liver through compromised liver function (Neuman *et al.*, 2006). Oxidative stress also plays an important role in hepatotoxicity in HIV-positive drinkers and alcohol further stimulates ROS formation (Bautista, 2001). Also, chronic alcohol consumption in HCV- or HIV-infected patient may synergistically affect the pro-inflammatory cytokine network, increasing the risk of developing hepatocellular carcinoma (O'Shea *et al.*, 2010). HAART can interact with alcohol or other drugs used for the prevention of opportunistic infections such as pneumonia, sexually transmitted diseases or tuberculosis leading to unwanted ADRs (Devito *et al.*, 2006; Hirbod *et al.*, 2006; Neuman *et al.*, 2012a).

HIV infection is the main risk factor for the reactivation of Tuberculosis into active disease. The risk of active Tuberculosis is elevated in individuals with alcohol abuse (Lönnroth *et al.*, 2008). Drug-drug interactions are possible between alcohol, anti-HCV, anti-HBV, anti-HIV and anti-TB medications (Neuman *et al.*, 2006). This has been especially reported for isoniazid metabolized by N-acetyltransferase 2 and CYP2E1 (Ellard, 1984). Alcohol and genetic polymorphisms could alter the activity of either of these enzymes and may influence the development of hepatotoxicity or enhance the toxicity of the isoniazid (Huang *et al.*, 2003).

ALCOHOL AND HISTAMINE H_2 RECEPTOR ANTAGONISTS

Manuela G. Neuman, Radu M. Nanau

Alcohol bioavailability has been shown to be lower when administered orally than through intravenous injection. This deviation suggests that alcohol undergoes substantial first-pass metabolism (Haber *et al.*, 1996; Chiang *et al.*, 2012). Lieber and colleagues have demonstrated that some histamine H_2 receptor antagonists (H_2RA) inhibit both gastric and liver ADH activity, resulting in decreased first-pass metabolism and increased blood alcohol levels (Caballería *et al.*, 1991; DiPadova *et al.*, 1992; Amir *et al.*, 1996). Cimetidine and ranitidine, which are H_2RA, can increase the peak levels of alcohol and the area under the alcohol concentration curve (DiPadova *et al.*, 1992). It was subsequently determined that the resulting elevations in blood alcohol levels were unlikely to exceed legal limits or be clinically relevant in individuals with adequate nutrition and with moderate social alcohol consumption (Raufman *et al.*, 1993; Weinberg *et al.*, 1998). A recent *in vitro* study and computer simulation confirmed that cimetidine can act either as a competitive or a non-competitive inhibitor, depending on the class of ADH isozyme. Cimetidine competitively inhibits class I ADH1, ADH2 and ADH3, and class IV ADH7, while it noncompetitively inhibits class I ADH2*2 and ADH2*3, and class II ADH4. Cimetidine also inhibits ALDH activity, namely ALDH1A*1, ALDH2 and ALDH3A*1, indicating that it interferes with both ADH and ALDH conversion steps in alcohol metabolism (Lai *et al.*, 2013). Since the cimetidine inhibition of ADH that is involved in ethanol metabolism is polymorphic, individuals who possess an ADH with low activity may accumulate an intermediate, which is then activated by CYP2E1 to hepatotoxins. Thus, the individuals ingesting ethanol and taking cimetidine in therapeutic doses might develop liver injury.

ALCOHOLIC LIVER DISEASE AND LIVER TRANSPLANTATION

Manuela Neuman, Lawrence Cohen

ALD is the second leading indication for liver transplantation, after chronic HCV infection (O'Shea *et al.*, 2010). According to the United Network for Organ Sharing database, 12.5% of liver transplant recipients between 1992 and 2001 were ALD patients. Five-year graft and patient survival of AH and alcoholic cirrhosis patients were 75 and 73%, and 80 and 78%, respectively, between 2004 and 2010 (Singal *et al.*, 2012). The 1-year patient survival for liver transplant patients was shown to be 85.5% in a large sample of liver transplant recipients (Krawczyk *et al.*, 2012). Many studies have shown that the patient survival rates, as well as graft survival rates, are comparable between patients with alcoholic cirrhosis and patients suffering from other liver conditions (Lucey, 2002; O'Shea *et al.*, 2010). Post-transplant graft and patient outcomes are better for patients with alcoholic cirrhosis compared with patients transplanted for HCV-related cirrhosis and are similar to other causes of end-stage liver disease and cirrhosis (Singal *et al.*, 2012). The cumulative 6-month survival rate was higher among patients who received transplantation within 2 months compared with individuals who did not receive the transplant in a sample of 26 patients with severe AH at high risk of death who showed no response to glucocorticoid therapy or presented rapid worsening of liver function despite medical therapy ($P < 0.001$) (Mathurin *et al.*, 2011).

Continued controversy surrounds the ethical issues of providing orthotopic liver transplantation for alcoholic individuals. The public gave low priority to alcoholic patients (Cohen and Benjamin, 1991; Mathurin *et al.*, 2011). Historically, these individuals are regarded as poor candidates to compete for the organs with others who are equally ill. These controversies arise due to an insufficient supply of donor organs compared with the demand.

Concomitant psychiatric disorders were identified as possible factors associated with recidivism after liver transplantation in a systematic review (McCallum and Masterton, 2006). Psychiatric and psychosocial evaluations should be required in the pre-transplant evaluation of patients, as well as during post-transplant follow-up, in order to treat alcoholism and prevent relapse (Varma *et al.*, 2010).

CONCLUSION

Alcohol-induced liver dysfunction spans a diverse array of topics. Alcohol metabolism involves several enzymes, including ADH, ALDH and CYP2E1, while chronic alcohol consumption is an inducer or the latter. Genetic polymorphisms as well as inter-individual variability in these enzymes mediate the risk of ALD. Moreover, CYP2E1 is involved in the metabolism of various xenobiotics, leading to potential drug–drug interactions and stimulating carcinogenesis. Alcohol should also be considered as immunogenic in infectious disease cases. Another important aspect of ALD disease progression is the co-morbidity with chronic viral hepatitis leading to increased fibrosis and inflammation. Further co-morbidities with HIV or with opportunistic infections such as tuberculosis are relatively common, while further interaction between alcohol and co-medications used to treat these conditions can exacerbate the degree of hepatotoxicity. The effect of alcohol on the adverse effects of a number of hepatotoxins, secondary to ethanol induction of cytochrome P-450 is an important additional hazard of alcohol intake, and suggests an important additional pathway for alcohol-associated liver damage. The interplay of these factors may explain the differential susceptibility to the development of ALD as well as of adverse drug reactions. A better understanding of the pathophysiological factors associated with ALD development by recognizing that ALD is the result of parenchymal damage leading to fibrosis, portal hypertension and

cirrhosis is valuable. In addition to treating the underlying disease, counseling can help increase alcohol abstinence, thereby improving the quality of life and increasing survival rates among ALD patients.

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