## Session VII

# Alcohol and Cytotoxicity

## Alcohol and Mitochondrial Function

Bernard Fromenty, Christine Demeilliers, Françoise Degoul, Abdellah Mansouri and Dominique Pessayre, INSERM U-481, Hopital Beaujon, Clichy, France

Mitochondria provide the major source of energy in the cell. The bulk of cellular ATP is produced by the oxidative phosphorylation (OXPHOS) process that feeds on reducing equivalents generated by numerous metabolic pathways, such as the mitochondrial ß-oxidation and the tricarboxylic acid cycle. Mitochondria have their own genome, the mitochondrial DNA (mtDNA), which encodes 13 proteins involved in OXPHOS. However, mitochondria are also the major source of reactive oxygen species (ROS) in the cell and they can commit cells towards necrosis and apoptosis through opening of the mitochondrial permeability transition pore (MPTP).

Alcohol intoxication is detrimental for several tissues, including the liver. Numerous evidences indicate that hepatic mitochondria are targets for ethanol toxicity and that ethanol-induced oxidative stress is a major mechanism involved in mitochondrial dysfunction. Indeed, ROS generated by ethanol metabolism can have deleterious effects on various mitochondrial components, including OXPHOS proteins, MPTP, lipids and mtDNA. Recently, we have shown that an alcoholic binge is responsible in mice for mtDNA depletion in the liver, but also in brain, heart and skeletal muscles. Several data suggest that hepatic mtDNA depletion is triggered by mtDNA damage such as strand breaks and abasic sites. Importantly, mtDNA depletion is only transient and normal hepatic mtDNA levels are recovered 4 hr after the alcoholic binge through efficient mtDNA replication (possibly associated with mtDNA repair). However, preliminary experiments performed in our laboratory indicate that a repeated alcoholic intoxication in mice induces prolonged hepatic mtDNA depletion (>48 hr) which may be due to impaired mtDNA replication. It is noteworthy that ethanol-induced mtDNA damage also occurs in humans. Indeed, multiple mtDNA deletions are found in the liver of alcoholic patients, mostly in alcoholics presenting microvesicular steatosis.

Taken together, these data indicate that ethanol intoxication presents detrimental effects on numerous mitochondrial components, thus leading to severe mitochondrial dysfunction. Strong evidence also suggests that ethanol-induced mitochondrial toxicity is involved in the physiopathology of diverse liver lesions such as microvesicular steatosis and alcoholic hepatitis.

## Immune Activation in Alcoholic Liver Disease

Dr RD Goldin, Department of Histopathology, Imperial College School of Medicine at St Mary's, London, UK

Immune mechanisms are important in producing alcohol induced liver damage and the systemic changes which accompany it. These mechanisms can be divided into antigen and non-antigen specific.

Neutrophils are the most characteristic inflammatory cell seen in alcoholic hepatitis but macrophages are increasingly seen as have a central role in initiating liver damage. IL-8, produced by hepatocytes, is important in attracting neutrophils to the liver which can produce a variety of inflammatory mediators. Kupifer cells are activated by endotoxin derived from the gut and subsequently release a variety of cytokines (including TNF, IL-1, IL-6 and TGF-ß) as well as reactive oxygen and nitrogen species. These factors can produce both local liver damage as well as the systemic changes associated with alcoholic liver disease. Anticytokine therapy has been successful in attenuating cell injury in animal models of alcohol liver injury. .The importance Kupifer cells in producing liver damage has been confirmed in animal models which the liver was depleted of macrophages and the liver damage caused by alcohol was attenuated.

Hypergammaglobulinaemia is a consistent finding and is predominantly IgA. Increased titres of autoantibodies are also seen in ALD. A preferential induction of Th2 vs. This immune response has been suggested, based on these increased immunoglobulin levels. There is an ongoing controversy about the presence of antibodies to liver-specific protein and Mallory's hyaline although antibodies to cytoskeletal structures are common. Antibodies to acetaldehyde modified proteins are also regularly detected. Circulating complexes have also been demonstrated and may play a role in producing systemic disease. Cell mediated immune mechanisms have also been implicated in producing alcohol induced liver disease. Both CD4 and CD8 positive, activated T cells have been demonstrated in the liver in alcoholic hepatitis. Claims

for increased peripheral blood CD4/CD8 ratios have been made. Natural killer cells and antibody-dependent cell-mediated cytotoxicity have also both been shown to be potentially important in producing hepatocytes damage.

## Bile Acids and Cytokines in Alcohol-Induced Cell Damage

Manuela G. Neuman

Division of Clinical Pharmacology, Sunnybrook and Women's College Health

Sciences Center, Toronto, Ontario, Canada

Caspases are intracellular cysteine proteases that are responsible for the apoptosis observed in numerous liver diseases. Destruction of the liver cells is rapid and extensive in the anti-fas antibody - and alcohol *in vitro* model of hepatitis, leading to liver cell death within hours. As previously shown, with 24 hours, human normal hepatocytes in primary cultures (HNH) and Hep G2 cells treated with 80 mM - 150 mM ethanol (EtOH) showed apoptosis. Cell death was attributed partially to inducibility of tumor necrosis factor (TNF-α) expression in cells and partially by the inability of the cells to detoxify the toxic metabolite of EtOH. Treatment of cells with ursodeoxycholic acid (UDCA) unable the cells to reduce TNF-α expression and therefore to reduce apoptosis.

The present work deals with Fas- as a pathway of alcohol-induced apoptosis and its possible blocking. Fas is a member of TNF family. Cells treated with 10 ug of antifas antibody resulted within two hours in a dramatic activation of caspase activity in soluble extracts of hepatocytes. The soluble caspase 3 that accumulated in apoptotic liver cells was measured by HPCL. Treatment of cells with a peptidebased, caspase 3 inhibitor (IDUN) protected against EtOH-induced apoptotic death in HNH and HepG2 cells. The present work identified UDCA as a molecule that might immuno-modulate apoptosis by faslanti4as pathway *in vitro.* 50 μM UDCA was found to inhibit recombinant caspase 3 but not caspase 9. UDCA exposure inhibited the caspase activity in soluble extracts from apoptotic cells *in vitro* and protected the cells from death as shown by TUNEL and electron microscopy methods.

## Interactions of Alcohol, Steatosis and Hepatitis C

L. Serfaty and R. Poupon

Service d'Hépatologie, Hôpital Saint-Antoine, Paris, France

Liver steatosis is a common histopathological finding in patients infected with hepatitis C virus. According to the "two hits" hypothesis proposed by Day et al, we postulated that patients with chronic hepatitis C having both steatosis and factors causing oxidative stress may be at higher risk of fibrogenesis. In a subset of patients with a definite date of contamination, our study was aimed as assessing the respective role of duration of infection and potential synergistic interaction between steatosis and factors susceptible to induce oxidative stress, namely alcohol intake, iron overload or drugs.

Among 700 anti-HCV positive screened patients, 142 untreated patients with liver biopsy and with one known risk factor (transfusion, IV drug use or Non-A Non-B acute hepatitis following blood exposure) were selected. A great care was taken to ensure a highly probable date of contamination by selecting patients with only one risk factor. None of the patients had liver injury suggesting alcoholic steatohepatitis or nonalcoholic steatohepatitis, except for steatosis. Each patient was reevaluated by a senior physician during follow-up visits using a standardized questionnaire containing 17 items. Any difference in the recorded data at the time of liver biopsy and during follow-up was resolved by a third evaluation and by consensus. Mean daily alcohol intake was assessed from the date of contamination until the diagnosis of HCV infection. Drinkers were defined as having a daily mean alcohol intake more than 30 g for men and 20 g for women. Regular use of drugs which are known to induce steatosis was assessed. Liver fibrosis, inflammation and necrosis were graded according to the Knodell score and steatosis as moderate to severe if more than 30% of hepatocytes were affected. Iron overload was assessed by Peris staining.

The severity of liver fibrosis was not related to the duration of infection between the date of contamination and the first liver biopsy (median 15 yrs). In multivariate analysis, two factors were independently associated with extensive fibrosis: the degree of severity of piecemeal necrosis (OR 3.27, CI:1.17-9.16), and combination of moderate to severe steatosis and alcohol intake (OR: 7.02, Cl: 1.1244). Independent parameters significantly associated with moderate to severe steatosis were BMI (OR: 1.13, Cl: 1.02-1 .26) and infection by genotype 3 (OR: 5.5, Cl: 1.88-16), but not alcohol consumption.

In summary, duration of infection has no major impact on the severity of fibrosis in hepatitis C. Besides the keyrole of severity of piecemeal necrosis, the study underlines the synergistic interaction between steatosis with an even low alcohol consumption as a contributor of extensive liver fibrosis. These results may have management implications in patients with chronic hepatitis C. Alcohol intake, and more generally factors susceptible to induce oxidative stress, should be avoided in patients having liver steatosis. It may be also speculated that intervention strategies to minimize oxidative stress should focus in patients with steatosis while antiviral treatment remains the treatment of choice in the subset of patients with severe interface hepatitis.

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## Session VIII

# Management of Alcoholic Hepatitis

## Nutritional Treatment of Alcoholic Hepatitis

Eduard Cabre, M.D.

Department of Gastroenterology. Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain

The outcome of alcoholic hepatitis (AH) varies with its severity. Whereas mild cases will easily recover by stopping drinking, the course of patients with severe disease (i.e. those with high serum bilirubin levels, prolonged prothrombin time, and/or spontaneous encephalopathy) is much poorer despite becoming abstinent, with a short-term mortality higher than 50%. Moreover, dietary intake in patients with mild disease is usually adequate, whereas severe patients remain anorectic for several weeks.

Several nutritional approaches have been assayed in the treatment of AH. The intravenous administration of standard amino acid solutions was firstly assessed in 1981 by Nasrallah and Galambos**,** who conducted a 4-week RCT on i.v. amino acid therapy in unselected patients with AH. They reported improved serum bilirubin and albumin levels, as well as decreased short-term mortality in those amino acid-treated patients ~. However, the number of women (known to have a poorer prognosis with AH) was greater in the control group. In fact, improved survival could not be reproduced by other authors. Moreover, the beneficial effects of amino acids on liver function test were marginal, and no definite changes in the histological appearance of the disease were observed in these studies.

The effects of total parenteral nutrition (PN) - including amino acids, dextrose and 10% lntralipid were compared to those of conventional diet, in a RCT where randomization was stratified according to the severity of the AH 4. Beneficial effects of parenteral nutrition were only observed in those patients with severe disease. Nevertheless, these effects merely consisted of a more rapid improvement in liver function, without any increase in short-term survival. The same results were found in a similar trial including only severe AH.

Two RCT have assessed the effect of adding enteral nutrition (EN) to the conventional diet, in unselected patients with AH (most of them with underlying cirrhosis). Both trials agreed in that enteral feeding improved the nutritional status but did not influence the short-term survival. However they were inconclusive regarding the effects of EN on liver function. Keams et *al.*[7] reported a more rapid improvement in serum bilirubin and encephalopathy in enterally fed patients. Interestingly, in a non-randomised study, the nutritional benefit was the same in patients with AH receiving EN than in those in whom this was contraindicated and were then treated with PN 5. Unfortunately, no RCT comparing EN vs PN in AH have been published yet.

The effects of 4-week treatment with either total enteral nutrition (TEN) or 40 mg/day prednisolone, upon the outcome of severe AH, have been recently compared in a multicentric RCT. No differences were found between both treatments in the survival rate during the treatment period, although deaths occurred earlier with TEN.

However, mortality was markedly increased (and mostly due to infections) in the immediate follow-up among those patients who had been treated with prednisolone, as compared to those being treated with TEN.

Artificial nutrition has been suggested to improve the effects of anabolic steroids, such as oxandrolone. Although not of benefit on short-term outcome, oxandrolone has been reported to improve long-term survival in patients with moderate (but not in those with severe) AH. Further studies suggested that the effects of oxandrolone would be more marked in those patients with an adequate nutritional intake, supplied either enterally or parenterally. There are no data available on a possible synergistic effect of artificial nutrition and corticosteroid therapy in severe AH.

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# Corticosteroids Improve Short Term Survival In Patients with Severe Alcoholic Hepatitis (AH): Individual Data Analysis of Randomized Placebo Double Blind Trials

Philippe Mathurin[1], Charles Mendenhall[2], Robert L Carithers J, Marie-Jose

Ramond[4], Willis C Maddrey, Peter Garstide[2], Sylvie Naveau[1], Jean-Claude Chaput[1],

Julien Taleb[6], Thierry Poynard[6]. [1]Hôpital Antoine Béclére, Clamart, France;

[2]Veterans Affairs Medical Center, Cincinnati, OH, USA;[3] Department of Medicine,

Seattle, WA, USA; Hôpital Beaujon, Clichy, France; Dallas Medical Center, USA;

Hôpital Pitié-Salpêtrière, Paris, France

Controversies surrounding the efficacy of corticosteroid treatment in patients with alcoholic hepatitis continue to persist. The aims of the present study on alcoholic hepatitis were: a) to analyze the individual data of patients with Maddrey discriminant function >32 (DF ≥ 32) from the three last randomized controlled trials; b) to identify the independent prognostic factors associated with short-term survival. **Methods** : The biological and clinical data were collected from the 3 principal investigators. Prognostic value of corticosteroid was estimated by survival at 28 days using the Kaplan-Meier method and compared by the log rank test. The independent prognostic values were assessed by the proportional hazards regression model. Results :102 placebo and 113 corticosteroid patients with DF ≥ 32 were analyzed. At the first day of treatment there were no significant differences between the 2 groups. At 28 days, corticosteroid patients (84.6±3.4%) had significantly higher survival than placebo patients (65.1±4.8%, p=0.001). In univariate analysis on overall patients (n=215), 5 variables reached a p value <0.1 as predictive factors of survival at 28 days: corticosteroids treatment (p--0.001), low age (p<0.0001), low DF (p=0.01), low serum creatinine (p<0.0001), high white blood cell counts (p=0.07) and absence of encephalopathy (p=0.01). In multivariate analysis, age (p=0.002), creatinine (p=0.03) and corticosteroids treatment (p=0.005) were independent variables that influenced the survival at 28 days. At 7 and 14 days a more important decrease of bilirubin was observed in corticosteroid than in placebo patients: -79.1±116.9 µmol/l vs -31.7±95.4 µmolIl and -122.5±138.8 µmol/l vs -57.1±129.5 µmol/l (p 0.03 and p-- 0.002). **Conclusion**: Corticosteroid improved the short-term survival of patients with severe alcoholic hepatitis. Age and serum creatinine were the other independent prognostic factors. Corticostenolds treatment is recommended for severe alcoholic hepatitis with DF ≥ 32. This is an example of false negative conclusions obtained by classical meta-analysis in comparison to analysis combining individual data.

## Alcoholic Hepatitis: No Glucocorticosteroids?

Christian Gluud

The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Glucocorticosteroids for patients with alcoholic hepatitis have been discussed in the medical literature for more than 30 years. The methodological quality and the results of randomised clinical trials evaluating glucocorticosteroids versus placebo or no intervention for alcoholic hepatitis differ substantially. This has led to disagreement regarding clinical practice. In 1992, 2% of European specialists in gastroenterologyl hepatology always used glucocorticosteroids for alcoholic hepatitis, 66% used it sometimes, and 32% never used it (Gluud et al., Gastroenterology International 1 993;6:221 -30).

Previously published meta-analyses on glucocorticosteroids for alcoholic hepatitis, using varying study inclusion criteria, have found a significant reduction in mortality by glucocorticosteroids. In the last published meta-analysis of 13 randomised clinical trials, we (Christensen and Gluud, Gut 1995;37:1 13-B) also found a significant reduction by glucocorticosteroids of the relative death risk within 3 months (0.57 (95% Cl 0.34-0.94 (random effects model)). However, the included randomised clinical trials were all small, the prognostic variables of the patients (age, encephalopathy, ascites, sex, and liver biochemistry) differed, and the individual trial results were significantly heterogeneous. According to a weighted logistic regression analysis adjusting for known prognostic variables, glucocorticosteroids did not significantly reduce the relative risk of death (0.73 (95% Cl 0.47-1.14)). Moreover, our meta-analysis showed evidence of publication bias and all the large sample trials found no significant therapeutic effect of glucocorticosteroids. Further, the methodological quality of a large proportion of the trials was low. Small randomised clinical trials of low methodological quality overestimates intervention efficacy by about 50% (Kjaergard et al., Cochrane Colloquium 1999;57: BlO).

New meta-analyses based on individual patient data from a selection of the published trials may demonstrate a beneficial effect of glucocorticosteroids on alcoholic hepatitis mortality. However, such meta-analyses are not based on all patients randomised. Accordingly, we need more information from meta-analyzing individual patient data combined with published group data from trials, from which individual patient data cannot be obtained, as well as from new randomised clinical trials before using glucocorticosteroids for alcoholic hepatitis. Otherwise, the debate will continue and patients may not receive the same high level of standard of evidence based medicine they deserve.

## Beneficial Effects of Polyenylphosphatidylcholine (PPC) in Alcoholic and Non-Alcoholic Liver injury.

CS Lieber, M.D. Section of Liver Disease and Nutrition, Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, USA

In liver diseases, already at the precirrhotic stage, there is a significant depression in the activity of phosphatidylethanolamine methyttransferase, an enzyme responsible for the production of phosphatidylcholine from phosphatidylethanolamine. Since phosphatidyl-choline constitutes the backbone of all membranes, its lack results in structural and functional abnormalities of these membranes, including deficient activities of the enzymes embedded in them, such as cytochrome C oxidase, a rate limiting step in the mitochondrial electron transport chain and in energy production. Replenishment of phosphatidylcholine through administration of PPC restored the activity of cytochrome C oxidase, the mitochondrial 03 utilization and the fatty acid oxidation. It also prevented the alcohol-induced fatty liver in rats and cirrhosis in baboons. Furthermore, PPC attenuated preexisting liver fibrosis and cirrhosis produced by $CCl_4$ in rats. The antifibrotic effects of PPC may be due, in part, to the down-regulation of the alcohol-inducible CYP2E1 and the associated antioxidant action, documented by a normalization of

markers of oxidative stress, such as F2-isoprostanes, malondialdehyde and Total Peroxyl Radical-Trapping Potential (TRAP), as well as to the decrease in the number of stellate cells activated to myofibroblasts-like cells responsible for the increase in collagen production. In cultured stellate cells, PPC also stimulated the production of collagenase which opposes collagen accumulation by promoting its breakdown. Many of the beneficial effects of PPC *in vivo* can be reproduced *in vitro* either by PPC itself or by its most abundant phosphati-dyicholine species, namely dilinoleoylphosphatidylcholine or DLPC, which has a high bioavailability. Because of PPC's experimental effectiveness and its total innocuity, 18 alcoholic volunteers at a pre-cirrhotic stage were randomly given 3 daily tablets of either 1.5 gram PPC or placebo, donated by Rhone-Poulenc Rorer & Co. (Cologne, Germany). PPC significantly ameliorated markers of oxidative stress *(vide supra).* After 2 years, liver fibrosis (assessed in sequential liver biopsies), showed progression in 5 of the 9 individuals given placebo but no change or regression in the 9 subjects treated with PPC (p<O.02). This promising pilot study is now being verified in an ongoing much larger multi-center, double blind, randomized trial.

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## Ursodeoxycholic Acid Treatment in Alcoholic Cirrhosis


RP Jazrawi, JMC Stenner, HA Ahmed, TC Northfjeld

Department of Gastroenterology Endocrinology and Metabolic Medicine, St.

George's Hospital Medical School, London, UK

It is estimated that 10-20% of people who abuse alcohol will get progressive liver damage. Thus, this condition is a major burden on health resources and a cause of significant morbidity and mortality for which there is currently no treatment other that the pursuit of abstinence.

UDCA, a hydrophilic bile acid, has been shown to be beneficial in cholestatic liver diseases, notably primary biliary cirrhosis (PBC). The exact mechanisms for its beneficial action are unknown. It has been suggested that through its choleretic action it reduces the effect of more toxic hydrophobic bile acids: that it can stabilize membranes: that it may have an immune modulatory effect and possibly an effect on the control of apoptosis. In PBC, UDCA has been shown to improve LFTs, delay the time to transplant and more recently to improve in liver histology. In addition, UDCA has been beneficial in rat models of cholestatic and alcohol induced liver disease. This supports data showing that UDCA results in an improvement in levels serum markers of hepatic fibrosis

The use and validity of serum markers of fibrosis is important because the "Gold Standard" of fibrosis assessment - a liver biopsy is not perfect. A biopsy is potentially dangerous, subject to sampling problems and it is difficult to get patient consent for repeated biopsies. It is for these reasons that serum markers of fibrosis have been proposed as suitable surrogates in the assessment of hepatic fibrosis. PIIINP, the N terminal peptide of procollagen Ill, typical for this class, is predominantly formed during the process of fibrosis and has been shown to correlate well with degrees of fibrosis in a number of conditions including alcoholic liver disease. However, single values lack the accuracy to replace liver biopsy in the assessment of fibrosis. Of more clinical use is the changes in serial measurements of PIIINP which have been shown to correlate with the corresponding changes in the clinical condition or other surrogate markers of liver function in alcoholic liver disease, methotrexate induced fibrosis and viral hepatitis. It is thus clear that fibrosis markers, while not perfect, can be used as surrogate markers of fibrosis and hence may be an important means of non-invasively assessing new treatments in liver disease.

The use of UDCA in alcoholic liver disease has not been extensively researched. This could be considered unusual given that alcoholic liver disease can typically present with the cholestatic features UDCA has been shown to reduce the cytotoxicity of alcohol in a cell culture model of alcoholic liver disease, however, to date there has been only two studies on the effect of UDCA in alcoholic cirrhosis. Plevris et al (EJGH, 1991), in a cross over trial of UDCA versus placebo in patients with alcoholic cirrhosis showed a significant improvement in ALP, GGT and bilirubin on UDCA. This was only a 1-month trial of UDCA and there was no assessment of fibrosis. In our own double blind randomised trial in alcoholic cirrhosis, over 6 months we also demonstrated a significant fall in ALP and GGT. In addition there was a significant reduction in the level of PIIINP on UDCA by comparison with placebo. This suggests, for the first time, that UDCA may have a beneficial antifibrotic effect in alcoholic liver disease. UDCA was well tolerated and caused no significant side effects. It is now necessary, as with the PBC studies, to carry out a long term study looking at the effect UDCA may have on morbidity and mortality in alcoholic liver disease.

## S-Adenosylmethionine in Alcoholic Liver Disease

J. Rodés

Liver Unit, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain

The efficacy of S-adenosylmethionine (SAMe) in the treatment of liver cell injury has been demonstrated in alcohol-induced liver damage and in other experimental models. In chronically alcohol fed baboons there is a significant depletion of SAMe, and SAMe supplementation restores the hepatic concentration of glutathione and other antioxidant systems. These systems will act as scavengers of toxic free radicals preventing lipid peroxidation and the development of liver damage. In human cirrhosis there is a similar impairment in methionine metabolism. Thus, SAMe could also be useful in cirrhotic patients. To evaluate the effect of SAMe in alcoholic liver cirrhosis, a randomized, double-blind trial was performed in 123 alcoholic cirrhotic patients treated with SAMe (1,200 mg/day, orally) or placebo for 2 years. Seventy five patients were in Child class A, 40 in class B, and 8 in class C. Sixty-two patients received SAMe and 61 received placebo. At the inclusion on the trial no significant differences were observed between the two groups with respect to sex ratio, age, Child classification and liver function tests. The overall mortality/liver transplantation at the end of the trial decreased from 30% in the placebo group to 16% in the SAMe group, although the difference was not statistically significant ($p=0.077$). When patients in Child C class were excluded from the analysis, the overall mortality/liver transplantation was significantly greater in the placebo group than in the SAMe group (29% vs 12%, $p=0.025$), and differences between both groups in the two-year survival curves were also significant ($p=0.046$). These results indicate that long-term treatment with SAMe may improve survival in patients with alcoholic cirrhosis, especially in those with less advanced liver disease. However, these encouraging data should be confirmed with a clinical trial including a larger and more homogeneous series of patients.