The Pervading Influence of Alcoholic Liver Disease in Hepatology

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Abstract — Rising levels of alcohol consumption in the UK are leading to substantial increases in morbidity and mortality from liver disease. Drinking is starting at an earlier age with binging an increasing common pattern, and women are overtaking men in the consumption. Manifestations of liver damage range from fatty liver to end-stage cirrhosis, but it is the increasing number of cases presenting with an acute alcoholic hepatitis (AAH) that are the cause for greatest concern. Development of well-validated prognostic scoring systems (Maddrey Modified Discriminant Function, Glasgow Alcohol Score) makes it possible to select those patients with AAH who are most likely to respond to corticosteroids. The results of early pilot studies of a number of anti-TNF agents are encouraging and for those deteriorating to the stage of liver failure, artificial liver support with MARS is of value in correcting major pathophysiological disturbances and as a bridge to liver transplantation, the results of which both for end-stage alcoholic cirrhosis and for AAH—of which there is limited experience, are excellent. Even as the stringent regulatory measures needed to control rising alcohol consumption are introduced by government, the burden of liver disease in the UK will remain high for years to come.

I feel greatly honored to have been awarded the Max Glatt Medal of the society of which he was the founding spirit. Max Glatt revolutionized attitudes to alcoholism in Psychiatry and introduced a new optimism as well as interest in the treatment of alcoholic patients. He was truly a leader and was a recipient of the Jellinek Prize, the most prestigious of the international awards in the field of alcohol. But my remembrance of him in his later years—and he was working up to shortly before his death at the age of 90 some 5 years ago, was of his compassion and charm, matched by his continued enquiring interest into the field for which he has done so much.

My title is well supported by facts, which with all the media publicity on the increase in alcohol consumption in this country and its effects will also be well known to you. Cirrhosis mortality rates for men increased by 104% in Scotland and 69% in England & Wales during the 1990’s and for women by 46% and 44%, respectively (Leon and McCambridge, 2006; Thomson et al., 2008). The cost to the NHS is horrifying—150,000 hospital admissions a year and according to a Royal College of Physicians report, a potentially hazardous alcohol intake identifiable in 20% of persons admitted with an unrelated illness. What is particularly disturbing is the earlier age at which people are starting to drink. Figures from the NHS Information Centre showed that in the year 2005–2006, the number of under 18’s admitted to hospital with alcohol-related conditions leapt by 13% to 8894. Women are overtaking men in their drinking habits and in a Salvation Army Alcohol Awareness Survey, 22% of 14–17-year-old girls admitted to binge drinking compared to 19% of the boys. Female gender has long been known to be an important factor in susceptibility to alcoholic liver disease. In an early study (Marbeth et al., 1987), 63% of the females developed cirrhosis compared with 33% of males at half the level of cumulative lifetime alcohol consumption (570 and 917 kg, respectively). The liver in adolescence may be particularly susceptible to alcoholic injury and this may apply to other organ damage. Evidence of reduced hippocampal volume and of permanent changes in brain activation has been discovered in adolescent-onset alcohol use disorders (De Bellis et al., 2000; Pascual et al., 2007). Binge drinking maybe particularly harmful as shown in one frightening experimental study I came across recently, which says brain damage and long-lasting neurobehavioral consequences could be induced in rats during their comparable adolescent period (Tapert et al., 2003).

Acute Alcoholic Hepatitis within Spectrum of Liver Damage

In the past descriptions of alcoholic liver disease (ALD) have focused on the occurrence of cirrhosis—usually in males after 30–40 years of heavy drinking and often not diagnosed until presentation with acute variceal bleed, or development of ascites and/or jaundice and encephalopathy. The asymptomatic early stages are characterized by markedly fatty liver and from this, cirrhosis can develop insidiously over the years as a result of ongoing liver cell necrosis, reactive inflammation, and fibrosis—so-called “steato-hepatitis” (Fig. 1).

But it is the increasing numbers of cases of AAH being encountered, which currently are of greatest concern. Seen more and more in younger age groups—tragically in women as early as the 30’s, AAH often follows a period of even heavier drinking. It presents as an acute illness with jaundice and is accompanied by all the features of an acute inflammatory reaction including fever, leucocytosis, and a high CRP (Forrest, 2007). The serum bilirubin is usually grossly elevated, although serum transaminase levels are only moderately raised, which can be of diagnostic help in distinguishing the condition from other causes of acute hepatic injury such as viral hepatitis or drug hepatotoxicity. Liver biopsy shows severe steato-hepatitis with macrovesicular fat, necrosis of liver cells, and characteristically a prominent neutrophil infiltration along with distinctive

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Liver damage from alcohol excess

Mallory bodies formed from damaged mitochondria. All gradations in histological changes are observed and in some 50%–60% of cases cirrhosis is already established. Twenty-eight-day mortality figures of up to 60% are quoted for the most severe cases, which progress to liver failure (Forrest, 2007).

The generation of oxidative stress is thought to have a central role in pathogenesis along with endotoxaemia from an increase in gut permeability. Kupffer cells are activated with stimulation of an inflammatory cell cytokine cascade and release of TNFα along with chemoattractants. The latter accounts for the marked neutrophil infiltration in the liver as part of the necroinflammatory reaction. In support of the important early role of TNFα release is the dramatic reduction in histological damage seen in the mouse model of AAH when a TNFα receptor 1 knockout animal is used.

VALUE OF CORTICOSTEROIDS AND ANTI-TNFα AGENTS IN AAH

The early observation of Maddrey and colleagues that corticosteroids could improve survival, presumably by controlling the inflammatory reaction, led to the Maddrey scoring system for estimating likely survival and its later development known as the Modified Discriminant Function (mDF) (Carithers et al., 1989). Another prognostic index was developed recently by workers from Glasgow based on scoring of white cell count and blood urea in addition to serum bilirubin and prothrombin time (Forrest et al., 2005). It gives an even higher level of prognostication with a better AUROC (area under receiver operating curve) than that obtained with the mDF (Fig. 2).

As to the value of corticosteroids in AAH arguments continue. Indeed since 1971 there have been four meta-analyses and 13 randomized studies. The most recent one—a reanalysis of data from the three largest and most carefully carried out randomized controlled trials in those with an mDF of >32, showed an overall survival at 28 days of 84.6% with corticosteroids compared to 65.1% for the placebo group (Mathurin et al., 2003). Sepsis and gastrointestinal hemorrhage are considered as contraindications and as a result many cases requiring treatment are excluded. However, Poynard argued cogently in a recent editorial that only by including these cases is there a chance of decreasing further the mortality of the condition. He points out that there is no scientific basis for these exclusions as corticosteroids are widely used by Intensivists for severe sepsis within the ICU setting and there is little evidence that GI bleeding is exacerbated by the use of corticosteroids (Poynard et al., 2003).

Recent trials give an additional and practically helpful dimension to the use of corticosteroids for it would appear that only in those cases where there is a fall in serum bilirubin by the end of the first week is survival improved. In the series of (Morris and Forrest, 2005) those cases having a 25% reduction in serum bilirubin after approximately a week’s treatment had a sustained improvement in outcome. Mathurin et al. (Mathurin et al., 2003) found that those with an early fall in bilirubin level—observed in 73% of the patients, had a 6-month survival of 83% compared to 23% in those in whom no fall was observed. (Louvet et al., 2007) developed this approach further in the “Lille Model,” in which an early bilirubin fall is combined with baseline laboratory data. This was shown to be highly accurate in prediction of longer-term benefit. Very recently the Glasgow group has published data showing, in an analysis of 225 patients with an mDF of >32, that significant benefit from steroids is obtained only in those additionally having a Glasgow Score of >9 (Forrest et al., 2007).

The recent studies from my Institute on the extraordinary susceptibility of patients with liver failure from AAH to infections, are also relevant to this consideration of corticosteroid usage. In an extension of early studies by us on neutrophil dysfunction (Rajkovic and Williams, 1985), the group has shown that full activation of the neutrophils as measured by oxidative burst with an accompanying marked reduction in phagocytic activity, is associated in AAH with significantly greater risk of infection, organ failure, and mortality. These changes in neutrophil function could be reversed in vitro by measures to lower plasma endotoxin. Patients with primed but not fully activated neutrophils are able to mount a response to further bacterial challenge and are likely to be at a lower risk from infections with steroids (Mookerjee et al., 2007b).

<table>
<thead>
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<th>Score</th>
<th>28 days survival</th>
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<tbody>
<tr>
<td>Maddrey* Modified Discriminant Function (mDF)</td>
<td>&lt;32</td>
</tr>
<tr>
<td>4.6x(PT prolongation secs.)* serum bil(μmol/L)&gt;17.1</td>
<td>≥ 32</td>
</tr>
<tr>
<td>Glasgow** Alcoholic Hepatitis Score (GAHS) on Day 1: Serum bil, PT, WBC &amp; blood urea (scored 1-3)</td>
<td>&lt; 9</td>
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<tr>
<td>&gt; 9</td>
<td>46%</td>
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Fig. 2. Maddrey Modified Discriminant Function and Glasgow Scoring systems for acute alcoholic hepatitis. (From data of Carithers et al., Ann. Intern. Med. 1989 May 1; 110(9): 685–90 and Forrest et al., Gut 2005 Aug; 54(8): 1174–9.)

*Carithers et al., 1989
**Forrest et al., 2005
As to other potentially effective therapies, the use of anti-TNFα agents in AAH is based on the sound experimental evidence of TNFα release from Kupffer cells playing a major role in the initiation of liver cell damage as referred to earlier. Early trials in man were encouraging. Pentoxifylline, an inhibitor of TNF synthesis, when given orally in a dose of 400 mg qds for 4 weeks was shown in a placebo-controlled trial to significantly decrease mortality (25% vs. 46%) with a marked reduction in frequency of the associated hepatorenal syndrome (Akriviadis et al., 2000). Of considerable interest is the report at the recent American Association for the Study of Liver Diseases (AASLD) meeting in Boston, that pentoxifylline in steato-hepatitis related to obesity rather than alcoholic intake leads to a reduction in hepatic steatosis, necroinflammation, and lobular inflammation in association with a reduction in TNF-α level (Singh et al., 2003). Etenecpt, which binds soluble TNF, is not so easy to use with the need for an intravenous loading dose and subcutaneous administration three times a week. A small pilot study of patients with high Maddrey scores reported a reduction of IL-6 at 2 weeks and an apparent increase in longer-term survival (Menon et al., 2004).

Initial resultswith the monoclonal anti-TNF antibody infliximab were particularly encouraging. In the study we carried out, patients received a single infusion of 5 mg/kg body weight at the time of admission to hospital (Tilg et al., 2003). Serum bilirubin levels decreased from a mean of 308 ± 127 to 131 ± 75 µmol/l at 28 days. Decreases in the proinflammatory cytokines IL-6, IL-8, and interferon gamma were also demonstrated. Ten of 12 cases with an mDF of 45 ± 7 survived. Infliximab has also been used in combination with corticosteroids. Using the same dose as we did, Spahr and colleagues (Spahr et al., 2002) showed a reduction at day 10 in IL-6 and IL-8 levels and a significant improvement in the calculated value mDF at 28 days. However, in the subsequent multicenter French trial of combined therapy in which three infusions of a much larger dose (10 mg/kg) were given at baseline, 2 and 4 weeks, there was a twofold increase in mortality and a high rate of infection which led to the trial being stopped after 36 patients had been entered (Naveau et al., 2004). Sadly, this result has so far prevented further trials of this potentially effective agent in controlling the initially damaging stage of TNFα release in AAH.

**Fall in portal pressure**

One of the striking improvements seen in the clinical monitoring of our infliximab-treated patients was a fall in portal pressure (Mookerjee et al., 2003). This occurred within 7–10 days of administration (Fig. 3). Raj Mookerjee from the Institute in studies on the mechanism involved has postulated that the inflammatory process of AAH leads to a rise in hepatic as well as blood concentrations of a substance known as asymmetric dimethylarginine (ADMA) by impairing activity of the enzyme DDAH responsible for its breakdown. ADMA is a known inhibitor of the enzyme endogenous nitric oxide synthase (eNOS) in the liver and as a consequence levels of hepatic vasodilatory substance nitric oxide fall leading to a rise in portal pressure. Infliximab, by decreasing the inflammation, leads to an increase in DDAH activity and to a reduction in the high ADMA levels, thereby lessening inhibition of eNOS and restoration of NO levels (Mookerjee et al., 2007a). Significantly higher serum

**Fig. 3.** Heparic venous pressure gradient (HVPG) values following treatment with Infliximab. (From Mookerjee R. P. et al. Gut 2003 Aug 52(8): 1182–7.) (Copyright permission received)

ADMA levels have been found in AAH patients than in those with alcoholic cirrhosis alone. In support of this hypothesis is the finding of a close correlation between ADMA blood levels and those of TNFα in patients with acute liver failure from a variety of etiologies (Mookerjee et al., 2007a).

**USE OF LIVER SUPPORT AND/OR TRANSPLANTATION IN LATER STAGES**

Measures to control the initial damaging processes in AAH by corticosteroids or by using anti-TNFα agents or other specific ligands to block the inflammatory cytokine cascade have the greatest potential for reducing severity and limiting progression of the condition. In those cases that do not respond to new techniques for temporary liver support may be of value in gaining additional time for spontaneous recovery or for transplantation to be effected. The most widely used of the current extracorporeal devices known as the Molecular Adsorbents Recirculating System (MARS) is based on dialysis of the blood against an albumin-impregnated high-flux membrane (Heemann et al., 2002). This has been shown to be highly effective in removing protein bound toxins from the blood. These are transferred across the membrane to bind with albumin in a recirculation circuit from which the toxins are finally cleared by passing through columns of adsorbent charcoal and anion exchange resin. I remember so clearly the first patient we treated at UCL (Fig. 4) (Jalan et al., 2003). Following admission—as so often happens, there was a relentless rise in serum bilirubin level despite withdrawal from alcohol and intensive supportive care. Each of the three MARS perfusions gave a reduction in serum bilirubin along with improvement in hepatic encephalopathy and he was finally well enough to be discharged from hospital.

The best controlled clinical trial of MARS carried out to date is that of Hassanein in the USA (Hassanein et al., 2007). The patients entered had advanced grades of encephalopathy from cirrhosis (including ALD). Albumin dialysis was carried out daily for 6 hours for up to five consecutive days. A two-grade improvement in hepatic encephalopathy (grade IV → II or III → I) was reached significantly faster
and more frequently in the MARS-treated than in the control group. Those showing this improvement also had a significantly improved survival. Decreases of blood ammonia, bilirubin, bile acids, creatinine, and other substances substantially raised in liver failure were documented and in a pilot study presented at the recent AASLD meeting on the tolerance and efficacy of the MARS system in AAH not responding to steroids, the reduction in serum bilirubin and creatinine levels was also statistically significant (Boitard et al., 2007). One notable finding amongst the many studies showing correction of the disturbed pathophysiology of liver failure by MARS (for recent review see Williams, in press) is a reduction in the often marked systemic vasodilatation from decreases in high levels of NO in the splanchnic and systemic circulations (Laleman et al., 2006).

**Place of liver transplantation**

For many people in the UK, carrying out a transplant for the consequences of alcoholism remains a sensitive issue. Indeed a UK survey showed that alcoholic liver disease was the most prevalent diagnosis among groups left to die without a transplant referral (Neuberger et al., 1998). For some of these patients this was because of physical or psychiatric comorbidity. In others it was probably more of a moral judgment based on the self-inflicted nature of the condition and of the perceived likelihood of a patient returning to his previous drinking habits. In fact, although some degree of recidivism is reported in 20%–50% of cases over 5 years after liver transplantation, no more than 15% return to heavy drinking and less than 5% develop severe liver injury. Adherence to the 6-month rule of abstinence prior to acceptance on the transplant waiting list means that some severely ill patients will die before satisfying that criteria. If abstinence is going to lead to an improvement in the patient’s clinical state—which is vital to determine, this is usually evident within 3 months (Veldt et al., 2002). Furthermore, family background, personality assessment, and work record are very often better indicators of the likelihood of significant recidivism post-transplant than adherence to a fixed term of abstinence (Foster et al., 1997).

Published results of transplantation for end-stage alcoholic cirrhosis, now the second commonest indication for a liver transplant worldwide, are excellent with survival figures similar to those for nonalcoholic cirrhosis (Tome and Lucey, 2003). Experience of transplantation in AAH is limited and indeed it is usually considered as a contra indication because of the patients’ dire clinical state as well as lack of a period of prior abstinence. The results in a series of 11 patients presented at the recent AASLD meeting are therefore of considerable interest. With a pretreatment median MELD score of 27.5, survival figures at 1, 2, and 5 years were 100%, 100%, and 82%, which compared favorably to those of other indications including alcoholic cirrhosis (90%, 88%, and 78%, respectively). The patients had been selected on the basis of a stable psychosocial environment and 9 of the 11 remained abstinrent long-term (Graziadei et al., 2007).

In conclusion, I hope you will agree that my title—*The Pervading Influence of Alcoholic Liver Disease in Hepatology*—is an appropriate one for the facts, figures, and findings that I have presented. Even if measures—inevitably stringent and unpopular—to contain the continuing rise in alcohol consumption in the UK are introduced by Government, the burden of liver disease in the country will remain high for years to come, with large numbers of patients requiring hospital and outpatient care for which additional facilities are urgently needed.

**REFERENCES**


