PTU-008 A REPRODUCIBLE, CLINICALLY-RELEVANT, INTENSIVELY-MANAGED, PIG MODEL OF ACUTE LIVER FAILURE FOR TESTING OF THERAPIES AIMED TO PROLONG SURVIVAL

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Introduction Hospitalisations from acetaminophen poisoning are increasing (1999, n=39 045; 2010, n=52 707. UK, NHS admissions). For the most serious cases there are no effective therapies to assist recovery or prolong survival apart from liver transplantation, which remains a limited resource. We report a clinically-relevant, intensively-managed, model of ALF, which mimics the human condition and has a predictable survival time, for testing of new potential therapies.

Methods Nine, 30–40 kg, female pigs were anaesthetised and instrumented for continuous monitoring and management of respiratory and cardiovascular systems and acid-base and electrolyte status, using standardised intensive care protocols and intermittent positive pressure ventilation. Intracranial pressure (ICP) was monitored but not treated. Six animals were induced to ALF with acetaminophen administered via an oroduodenal tube: a loading dose of 0.25 g/kg was followed by hourly doses of 0.5–4.0 g adjusted according to serum acetaminophen concentrations. At irreversible ALF (defined as prothrombin time >3 times normal), continuous renal replacement therapy (CRRT) was initiated. Three animals acted as controls with initiation of CRRT at 20 h and termination at 40 h.

Results Following onset of acetaminophen dosing, peak serum acetaminophen concentrations of 367±30 mg/l were achieved at 12 h and irreversible ALF at 19.3±1.8 h. Death occurred predictably 12.6±2.7 h after irreversible ALF. Development of ALF was associated with progressive hypotension ($p<0.001$) and metabolic acidosis ($p=0.001$), not observed in controls. Mean arterial pressure (MAP) was maintained with aggressive fluid therapy, noradrenaline and terlipressin. Metabolic acidosis was corrected successfully with bicarbonate and CRRT. In ALF, there was significant ($p<0.001$) rise in ICP compared to controls with sudden marked increase prior to death: at study end, ICP in ALF and controls was 41.2±8.6 mm Hg and 22.7±2.5 mm Hg respectively. Death was preceded by abrupt increase in central venous pressure, fall in MAP and bradycardia. Histopathology confirmed moderate to marked acute centrilobular to midzonal hepatocyte degeneration and necrosis in ALF.

Conclusion A predictable model of ALF, with death due to multi-organ failure, has been successfully validated for translational studies for therapies designed to prolong survival in man.

Competing interests None declared.

PTU-009 ALCOHOL-INDUCED LIVER TOXICITY IS ASSOCIATED WITH NEUTROPHIL DYSFUNCTION IN A NOVEL IN-VITRO MODEL OF ACUTE LIVER INJURY

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Introduction Sepsis is a major cause of mortality in patients with alcohol-induced acute and chronic liver failure (ALF/CLF). Neutrophils are a major innate immune cell subset involved in the first line of defence against infection and circulating neutrophil dysfunction has been reported in patients with ALF/CLF. However, there is a paucity of understanding regarding the mechanisms involved in this dysfunction. In this study we aimed to characterise the precise relationship between neutrophil dysfunction and alcohol-induced liver damage with a novel in vitro model mimicking the in vivo interactions of neutrophils and hepatocytes.

Methods We cultured a well-characterised neutrophil-line HL-60 either directly with ethanol or with supernatants taken from ethanol metabolising-human hepatoma cell lines VL-17A (positive for alcohol-dehydrogenase and CYP2E1) cultured in the presence of safe levels (10 mM) and toxic levels (250 mM) of ethanol reflecting real-life human alcohol consumption for 24 h. Neutrophil function was evaluated by TLR expression, chemotaxis, phagocytosis and respiratory burst assays. Cell supernatants were also collected for cytokine profiling and to quantitate levels of ammonia and ethanol metabolites. The effect of ethanol on the functional activities of neutrophils isolated from both normal and ALF/CLF patients will also be assessed.

Results Supernatants collected from the hepatoma line VL17A cultured with 250 mM ethanol (representative of an alcohol binge) significantly reduced the phagocytic capacity of the HL-60-neutrophil line ($p<0.05$). This was greater than the effect of the same concentration of ethanol applied directly to the neutrophils ($p<0.05$). Our preliminary data also suggests that the metabolised ethanol inhibits chemotaxis of the HL60-neutrophil cells towards a gradient of fMLP. Furthermore, we observed a reduction of TLR4 expression.

Conclusion We describe a novel model for investigating the correlates of dysfunctional innate immunity during acute alcohol-induced liver injury. We identify that alcohol does impair neutrophil function directly but this is profoundly increased after hepatocyte alcohol metabolism implicating a causal link between liver injury and impairment of antibacterial neutrophil functions.

Competing interests None declared.

PTU-010 COMPUTATIONAL MODEL PREDICTS THAT PORTOSYSTEMIC SHUNTING IS KEY TO THE DEVELOPMENT OF HYPERAMMONAEMIA IN LIVER CIRRHOSIS

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Introduction Hyperammonaemia occurs in patients with advanced cirrhosis, which is also associated with a major redistribution of blood flow (hyperdynamic circulation). Previous investigations have sought to explain hyperammonaemia on the basis of metabolic adaptation (enzymatic derangements). We hypothesised that hyperammonaemia is centrally linked to the haemodynamic disturbances caused by portal hypertension. To test this hypothesis, we developed a theoretical model, which predicted arterial ammonia levels when organ blood flow is modulated.

Methods Assumptions on individual organ fluxes of ammonia (across the gut, liver, muscle, brain and kidney) were based on published arterio-venous differences and tracer kinetic data. In order to study the role of organ blood flow in isolation, we assumed that hepatic detoxification function and ammonia production were normal. A wide range of conditions was investigated (increased cardiac output, splanchnic vasodilation, low to high porto-systemic shunt fraction). In addition, we used scenarios of organ blood flow corresponding to Child Pugh A, B and C. Finally, we considered the effect of lowering ammonia release in the renal vein.

Results Hyperammonaemia developed when the fraction of gastrointestinal blood shunted was more than 65%. The influence of

redistribution of organ blood flow accounted for <10% of the increase in arterial levels. Decrease in ammonia release in the renal vein may be sufficient to compensate for the increase in arterial ammonia due to shunted flow in Child Pugh A and B, but is insufficient in stage C.

Conclusion Portosystemic shunting may be centrally involved in the generation of hyperammonaemia in liver cirrhosis. This can be partially attenuated by increased urinary ammonia excretion. In patients with cirrhosis, decreased hepatic functions and metabolic changes may further increase the arterial ammonia levels.

Competing interests None declared.

PTU-011 A NEW CONCEPT TO EXTEND RESECTABILITY OF LIVER TUMOURS: TWO STAGE SURGICAL STRATEGY USING AN IN-SITU-SPLIT PROCEDURE

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Introduction Today only 20%–25% of colorectal liver metastasis are resectable at initial presentation, despite the progress made in liver surgery over the last 25 years.[1] The induction of liver hypertrophy by preoperative portal vein occlusion (Embolisation or Ligation) is the most used tool to prevent postoperative liver failure allows a Future Liver Remnant (FLR) growth of up to 20%–35% in 45 days.[2] For 1 year we have engaged a new method of achieving resectability in patients affected by extensive disease involving both lobes with insufficient future remnant liver volume (FRLV).[3]

Methods Between March and November 2011 six patients affected by liver tumours (4 colorectal liver metastasis (CRLM), 1 GIST-metastasis, 1 gallbladder carcinoma) were judged to be irresectable because of an insufficient RLV (<20%). Therefore all those patients were submitted to a two staged procedure: (1) Right portal vein ligation, in situ split procedure and additionally atypical resection of a metastasis in the FRL if needed. After CT controls with 3D reconstruction and volumetry (2) Extended right hemi-hepatectomy.[3]

Results Resectability was achieved in all patients around 2 weeks after step 1 (range 10–21 days). In five patients the FRL gained about 66% in volume (range 45%–95%); the patients were operated and discharged without complications. One Patient (gallbladder carcinoma)—despite good volumetry (42%)—suffered severe cholangitis postoperatively and died of consecutive liver failure 58 days after the second step operation.

Conclusion This method showed to be effective in patients initially judged to be irresectable. One possible explanation could be that the in-situ liver transection, causing disruption of intrahepatic portal collaterals, increases portal flow deprivation to the excluded segments and redistribution of hepatotrophic factors, accelerating future remnant liver growth. Patients with jaundice from biliary tract tumours seem not to be good candidates for this approach. The proposed new strategy has had value in extending resectability in patients suffering from extensive CRLM,[3] reducing the risk of postoperatory liver failure, in our preliminary experience, more than other established methods.

Competing interests None declared.

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PTU-012 THE IMPACT OF COMORBIDITY ON POST LIVER TRANSPLANT SURVIVAL AND RESOURCE UTILISATION IN PATIENTS TRANSPLANTED FOR ACUTE LIVER FAILURE UTILISING THE CHARLSON COMORBIDITY INDEX

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Introduction The presence of comorbidities negatively impact post liver transplant (LT) survival for those transplanted with chronic liver disease.

Methods assess the impact of comorbidities on survival in patients transplanted for acute liver failure (ALF).

Results 176 patients underwent LT for ALF over 9 years. Median follow-up was 92 months (range 35–142). Median age was 33 years (17–67) and 122 (69.3%) were females. Fifty-nine patients (33.5%) were transplanted for Paracetamol induced ALF. Ninety-six (54.6%) patients had ≥1 comorbidity. The commonest comorbidity was renal dysfunction in 84 (48%), pulmonary disease in 10 (6%), connective tissue disease in 5 (3%) and 2 (1%) had diabetes. Patients with ≥1 comorbidity had significantly increased 6 month (25% vs 13%, p=0.046), 12 month (27% vs 13%, p=0.023) and overall mortality (32% vs 17%, p=0.019). Similar results were demonstrated for graft survival. Recipient age ≥ 40 years (OR=1.37, 95% CI 1.02 to 1.86, p=0.039), the presence of comorbidity (OR=1.46, 95% CI 1.05 to 2.03, p=0.022) and renal dysfunction (OR=1.62, 95% CI 1.18 to 2.23, p=0.003) were associated with increased post LT mortality on univariate analysis. However, only the presence of comorbidity (OR=1.43, 95% CI 1.03 to 1.98, p=0.032) and renal dysfunction (OR=1.59, 95% CI 1.15 to 2.19, p=0.004) were independently associated with mortality. Other recipient related, donor, or graft variables were not associated with mortality. Patients with ≥1 comorbidity had significantly increased ICU length of stay (LoS) of 20 days (3 to 134) compared to those without comorbidities, 16 days (2–102), p=0.005.

Conclusion Pre- LT comorbidity as defined by the presence of ≥1 comorbidity, significantly impairs overall post-LT patient and graft survival in patients transplanted for ALF. Patients with ≥1 comorbidity had significantly increased ICU LoS which may suggest increased resource utilisation.

Competing interests None declared.

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PTU-013 SINGLE USE OF ROMIPLOSTIM THROMBOPOIETIN ANALOGUE (TPO) IN SEVERE THROMBOCYTOPAENIA FOR OUTPATIENT PERCUTANEOUS LIVER BIOPSY IN PATIENTS WITH CHRONIC LIVER DISEASE (CLD): A RANDOMISED DOUBLE BLINDED PROSPECTIVE CLINICAL PILOT TRIAL

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Introduction Thrombocytopaenia is a common entity in CLD with or without cirrhosis. Liver biopsy is the gold standard for diagnosis and prognosis of CLD. Platelet count is imperative before percutaneous liver biopsy. Platelet transfusion requires over night hospitalisation with transfusion associated morbidities and cost burden.