Their expression of CXCR3 provides a potential mechanism for recruitment into the tumour environment.

Competing interests None declared.

BASL plenary session

OC-022 EMBOLISATION OF INFLOW TO ALLOW SAFER LIVER RESECTION—IS MORE, BETTER?

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Introduction Portal vein embolisation (PVE) is now an established technique to increase the future liver volume/remnant (FLR) prior to liver resection. For those patients where hypertrophy is still considered insufficient complete uni-lateral embolisation incorporating both portal and hepatic artery embolisation (HAE) has been less frequently reported. The aim of this study was to evaluate the feasibility of sequential PV/HA embolisation to increase the FLR prior to liver resection.

Methods All HPB patients are discussed at a weekly MDT meeting to decide on appropriate management decisions including the necessity for FLR augmentation. PVE is performed by initially obtaining a portogram by percutaneous trans-hepatic puncture. Selective embolisation of the necessary portal veins are then performed using a combination of coils and glue etc. Embolisation of Segment 4 PV branches are performed on a selective basis. HA embolisation is performed by mapping arterial inflow and selectively embolising the desired segments planned for resection while carefully preserving the FLR. The aim of this study was to evaluate the feasibility/safety of PVE with sequential HAE over a 5-year period (January 2006–May 2011).

Results 50 patients (M:F = 38:12) underwent a right PVE; 33 (66%) progressed to liver resection. Reasons for inoperability (34%) following PVE (n=17) were (1) Small FLR, (n=6) all underwent HAE (with five proceeding to liver resection) (2) extra-hepatic disease (n=7) (3) progression of hepatic disease (n=4). The median FLR of those who progressed to resection following PVE, by CT volumetry, was 384.5 cc (330–490), significantly more than those who did not 237 cc (110–280) p=0.03. HAE increased the FLR by a further 99.8 cc (range 80.5–130 cc). An R0 resection was achieved in 25 patients (76%), including 4/5 (80%) of sequential patients. Following PVE and sequential embolisation; 9/33 (27%) and 3/5 (60%) suffered serious complications (Clavien-Dindo 3 or 4). There were six post operative deaths including 5/33 (15%) after PVE and 1 (20%) following sequential embolisation respectively.

Conclusion PVE is an increasingly used technique to increase the FLR allowing a significant proportion of patients an R0 resection despite initially being considered inoperable. Nevertheless at least 20% of patients will also have progression of disease. Patients who do not achieve adequate hypertrophy can potentially have HA embolisation to increase the FLR by a further 100 cc but perhaps at the expense of increasing post-operative complications.

Competing interests None declared.

OC-023 EXTRACORPOREAL LIVER SUPPORT USING UCL-ARSENEL REDUCES INFLAMMATION, IMPROVES HAEMODYNAMIC FUNCTION AND INCREASE SURVIVAL TIME IN A PORCINE PARACETAMOL-INDUCED ACUTE LIVER FAILURE MODEL

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Introduction Though the incidence of liver disease continues to increase, an effective liver support device remains an unmet clinical need. We have demonstrated that in liver failure, albumin function is irreversibly damaged, preventing detoxification processes, and that bacterial endotoxins induce systemic inflammation and neutrophil dysfunction. To date, toxin removal devices have failed to demonstrate clinical efficacy, which may be due to an inability to address albumin damage and/or inflammation. An albumin replacement system with a novel endotoxin ligation (ARSeNEL) component was developed to selectively to adsorb endotoxin and replace damaged albumin in patients' plasma.

Methods We tested the device in an acetominophen model of acute liver failure (ALF). 16 female landrace pigs (eight ALF, five ALF + UCL-ARSeNEL) were studied. Irreversible ALF was induced by acetaminophen administration via a jejunel catheter, confirmed by deranged clotting function (PT >30% normal). Treatment was with UCL-ARSeNEL or CVVH control within 2 h of ALF confirmation. The ARSeNEL device consists of three components; plasmapheresis, endotoxin and high cut-off (100 kDa) filters; with fresh frozen plasma replacing ultrafiltered plasma. Endpoints were: survival; ICP; heamodynamic parameters, standard biochemistry; cytokines; albumin damage; and plasma endotoxin levels.

Results UCL-ARSeNEL significantly increased survival post ALF (ALF 15.8±2.4 h vs UCL-ARSeNEL 23.8±1.9 h; p=0.02). Endotoxin reduced by a quarter (1.99±0.18 Eu/ml vs 1.42±0.21 Eu/ml) in the device group at 16 h. The changes in ICP index (1.7±0.07 vs 1.4±1.58), INR (16.6±6.6 vs 6.8±0.5), ischaemia-modified albumin ratio (0.45±0.166 vs 0.35±0.108), noradrenaline requirement (61.11±15.4 vs 28.7±15.2 μg/Kg), and mean arterial pressure (71±7.6 vs 87±6.0 mm Hg) showed marked improvement in the UCL-ARSeNEL group. Measured inflammatory cytokines IL8, IL6, IL1b, TNFa and neutrophil activation (spontaneous burst p=0.03) were all found to be reduced in the ARSeNEL treated group compared with ALF control.

Conclusion These results confirm that UCL-ARSeNEL improves survival in ALF by addressing key pathophysiological derangements such as albumin dysfunction and endotoxinaemia; which impact upon systemic inflammation and end-organ function. The reduction in inflammation is associated with improved vascular function and reduced inotropic support requirements.

Competing interests None declared.

OC-024 DEVELOPMENT AND VALIDATION OF A NOVEL CAPTURE-FUSION MODEL FOR HCV REPLICATION

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Introduction HCV replicates poorly in vitro, so testing of novel antiviral therapies currently relies on modified viral replicons, based on genotype (G)1, or the G2 JFH-1 virus. A model allowing patient virions to be cultured would facilitate drug discovery and allow direct sensitivity testing. Here we describe the development of a novel HCV replication assay, its validation using the antiviral agents alisporivir and telaprevir and its value in identifying responses to interferon and ribavirin.

Methods CD14 (+) monocytes derived from patients with chronic HCV infection, or pre-stimulated THP-1 cells infected with serum from G1 and G3 HCV infected donors, were fused with HuH7 cells and treated with antiviral agents at various concentrations. The fused cells were maintained in tissue culture for up to 5 days, before

extraction of HCV RNA and quantification by PCR. p Values were derived using the Mann–Whitney U test for comparison of non-parametric data. Results are expressed as mean±SEM.

Results Replicating HCV from patients infected with diverse genotypes could be successfully transferred to HuH7 cells using the monocyte "capture-fusion" approach. RNA increased fivefold in fused cells and viral protein production as well as viral release could be demonstrated, confirming the presence of complete viral replication cycles in this new model. Treatment of G1 and G3 fused/infected Huh7 cells with escalating concentrations of alisporivir showed greater drug efficacy in cells infected with G3 than G1 (IC_{50} 0.026±0.008 μM vs 0.109±0.02 μM, p=0.0286). Conversely, telaprevir showed greater efficacy in fused/infected cells with G1 than fused/infected cells with G3 HCV. Treatment with 0.1 μM telaprevir, which approximates its IC_{50} in replicon cells, resulted in a reduction of HCV RNA by 66.15±10.43% in G1 cells vs 21.56±3.16% in G3 infected cells (p=0.016). We examined sensitivity to interferon and ribavirin in samples from patients who did (N=3), or did not (N=4), respond to therapy. We found no significant difference in the viral sensitivity, suggesting that for interferon based therapies host factors play a more important role than virological response.

Conclusion These data confirm the value of a capture-fusion model for HCV replication in studying the replication of patient-derived HCV and demonstrate that for interferon and ribavirin based treatments, host factors dominate the response. However viral response determines the clinical response to direct acting anti-viral agents. This technique may be useful in identifying the most appropriate treatment strategies for patients with HCV planning therapy with the new direct acting antiviral agents.

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OC-025 ALISPORIVIR INHIBITION OF CELLULAR CYCLOPHILINS DISRUPTS HEPATITIS B VIRUS (HBV) REPLICATION AND THIS EFFECT IS FURTHER ENHANCED IN COMBINATION WITH DIRECT ANTIVIRAL TARGETING HBV-DNA POLYMERASE IN VITRO

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Introduction Cyclophilins are intracellular proteins with enzymatic activity—peptidyl-prolyl-isomerase that plays a major role in the life cycle of Hepatitis C virus. By targeting host cyclophilins Alisporivir (DEB025) exerts potent anti-HCV activity in vitro and in clinical studies. We have recently shown in vitro that cyclophilin inhibition with Alisporivir or NIM811 also interferes with HBV replication, with Alisporivir having a greater effect than NIM811. To elucidate the underlying mechanisms, in the present study we compared in vitro the effects on HBV replication of Alisporivir alone, Alisporivir in combination with a potent antiviral targeting HBV-DNA polymerase, and in cells after selective knockdown of individual cyclophilins.

Methods Stably (HepG2215) and transiently (HUH-7) transfected cells, producing full HBV virions and HBsAg particles, were treated with different Alisporivir concentrations (0.25/1.0/5.0/20 ug/ml) alone, Telbivudine alone, or combinations of Alisporivir and Telbivudine. To determine the involvement of individual cyclophilins, HepG2215 cells were transfected with siRNA-specific for cyclophilin (Cyp) A, C or D and additionally treated with Alisporivir. Cytoplasmic extracts and supernatants were harvested at baseline; 24, 48 and 72 h post-treatment. The kinetics of antiviral activity was assessed by quantitation of intracellular and secreted HBV-DNA (real-time qPCR) and HBsAg levels (ELISA).

Results Alisporivir treatment resulted in dose-dependent reduction of intracellular and secreted HBV-DNA from HepG2215 and HUH-7 cells at all time points, by 70% (p=0.004) and 63% (p<0.001), respectively, compared with untreated controls. The combination of Alisporivir and Telbivudine had greater effects in reducing intracellular (p=0.001) and secreted (p=0.028) HBV-DNA, and >3-fold reduction of HBsAg vs either Alisporivir or Telbivudine alone. CypA, C or D expression was markedly reduced after transfection with corresponding siRNA, which was associated with significant decrease of HBV-DNA and HBsAg levels (p<0.001). Alisporivir treatment of cells silenced for CypA, C or D further reduced HBV-DNA and HBsAg levels, with greater antiviral effects in CypC or CypD silenced cells, compared with CypA silenced cells (p<0.001).

Conclusion These results suggest that Alisporivir interferes with multiple sites of HBV replication and has synergistic antiviral activity with direct antiviral targeting viral DNA polymerase, such as Telbivudine.

Competing interests None declared.

Service development free papers

OC-026 PREDICTING COMPLICATIONS IN LIVER SURGERY

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Introduction Cardiopulmonary Exercise Testing (CPET) is a non-invasive test that has been used to identify patients at higher perioperative risk. Studies have found that different CPET variables seem to be more predictive in different patient groups. There is little literature on the use of CPET within the HPB field, and no series concentrating on patients undergoing Liver resection. Our aim was to identify the most sensitive CPET variable for risk prediction in this patient group.

Methods From 1 October 2009 CPET was carried out in all patients due to undergo Liver resection meeting one or more of the following criteria (1) planned extended right/or extended left resection (2) over 65 (3) significant comorbidities. Data were prospectively entered into a database. This was correlated with preoperative CPET data and analysed using version 19 of SPSS.

Results Between 1 October 2009 and 1 July 2011 188 patients underwent Liver resection, 121 (64%) underwent CPET (Group A), and 67(36%) did not (Group B). Group A were older (mean age 70 vs 54) and had higher complication rates (56% vs 36%) and had longer length of stay (median 7 vs 5) (all p<0.001). The three deaths occurred within group A. Multivariate analysis of Group A including age, BMI, extent of surgery (segments), VO_2 at anaerobic threshold (AT), VO_2 peak, O_2 pulse, and heart rate found that O_2 pulse at AT, and HR at AT correlated best with a risk of increased complications. OR O_2 pulse 0.86(CI 0.72 to 1.01, p 0.07), HR at AT 1.04 (CI 1.001 to 1.06, p<0.01).

Conclusion This is the largest study of CPET in the HPB field, and the only study involving only Liver resection. CPET can be used to identify those at higher perioperative risk, with O_2 pulse and HR at the Anaerobic Threshold the most sensitive indicators. The selective use of CPET was justifiable as all patients who died in the post-operative period were identified. Complications still occurred within the non-CPET cohort suggesting expansion of CPET selection criteria may be needed.

Competing interests None declared.