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.

Competing interests M Cunningham: None declared, A Javaid: None declared, J Waters: None declared, G Foster grant/research support from: Roche, Janssen, Tibotec, Novartis, Consultant for: Abbott, BI, BMS, Chughai, Janssen, Merck, Novartis, Roche, Tibotec.

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

doi:10.1136/gutjnl-2012-302514a.25

[1]S Chokshi,* [1]S Phillips, [1]A Riva, [2]N Naoumov. *[1]Foundation for Liver Research, Institute of Hepatology, London, UK; [2]Novartis Pharma AG, Novartis, Basel, Switzerland*

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

doi:10.1136/gutjnl-2012-302514a.26

[1]D Dunne,* [2]F Pilkington, [1]R Jones, [1]H Malik, [1]G Poston, [3]D Palmer, [4]S Jack, [1]S Fenwick. *[1]Northwestern Hepatobiliary Centre, Aintree University Hospital, UK; [2]School of Medicine, University of Liverpool, Liverpool, UK; [3]Department of Oncology, University of Liverpool, Liverpool, UK; [4]Department of Respiratory Medicine, Aintree University Hospital, Liverpool, UK*

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.