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 POLYMERSASE IN VITRO

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

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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 or NIM811 and observed that Alisporivir and NIM811 interfered with HBV replication, with Alisporivir having a greater effect than NIM811.

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.

OC-026 PREDICTING COMPLICATIONS IN LIVER SURGERY

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

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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), VO2 at anaerobic threshold (AT), VO2 peak, O2 pulse, and heart rate found that O2 pulse at AT, and HR at AT correlated best with a risk of increased complications. OR O2 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 O2 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 postoperative period were identified. Complications still occurred within the non-CPET cohort suggesting expansion of CPET selection criteria may be needed.

Competing interests None declared.

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