P50 APOLIPOPROTEIN E AND LOW-DENSITY, APOLIPOPROTEIN B ASSOCIATED LIPOVIRAL PARTICLES IN CHRONIC HEPATITIS C INFECTION: EVIDENCE FOR GENOTYPE-SPECIFIC MODULATION OF LIPID PATHWAYS

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Introduction Hepatitis C virus (HCV) co-opts the VLDL assembly, maturation, degradation, and secretory machinery of hepatocytes. Infectious low density particles have been termed lipoviral particles (LVP). LVPs in vivo are triglyceride (TG) rich and contain at least viral RNA, HCV core protein and the VLDL components apolipoprotein B (apoB) and apoE. ApoE is a constituent of infectious HCV particles produced in cell culture, and production of infectious particles is dramatically impaired from cells in which apoE expression has been genetically silenced.
Aim To examine the relationship between LVP and apoE in vivo.
Method Fasting plasma samples were obtained from 39 chronic HCV genotype (G) three patients and 51 HCV G1 patients. LVP were measured using iodixanol density gradient ultracentrifugation as recently described.[1] ApoE levels were determined by an automated immunonephlometric method. Demographic data were recorded and liver biochemical tests, lipid profiles and HOMA-IR were measured in all patients.
Results The mean LVP in HCV G3 was 5.2 log10 IU/ml with a mean LVP ratio of 0.286, but showed wide variation (0.03–0.96). This was not significantly different to LVP variation in HCV G1 we have previously reported.[1] In HCV G1 we found a strong positive correlation of LVP HCV RNA with apoE levels (r=0.488, p=0.001) and also with LVP ratio (r=0.428, p=0.001). In contrast in HCV G3 we found a significant negative correlation of LVP HCV RNA with apoE levels (r=−0.428, p=0.013), suggesting different utilisation of lipoprotein pathways. We also found a negative correlation of LVP in HCV G3 with HDL cholesterol (r= −0.468, p=0.003) and its structural lipoprotein apoA1 (r= −0.479, p=0.002) whereas we have reported no correlation of LVP in cHCVG1 with HDL or apoA1.[1] Furthermore in HCV G3 we found low TG levels compared to G1 (1.00±0.71 vs 1.35±0.76) and no correlation of LVP with TG or HOMA-IR, again contrasting to G1 infection[1].
Conclusion This study suggests that while serum apoE quantity is a positive determinant for LVP quantity in HCV G1 infection, it is a negative determinant in HCV G3 infection. Furthermore, LVP quantity in HCV G3 is largely based on the paucity of HDL quantity and their components, rather than the parameters associated with TRL levels as in HCV G1. These differences highlight that interaction with host lipoprotein metabolism is important for HCV infection in different genotypes, but in genotype specific ways.

REFERENCE

1. **Bridge SH,** *et al*. Insulin resistance and low-density apolipoprotein B-associated lipoviral particles in hepatitis C virus genotype 1 infection. *Gut* 2011;**60**:680–7.

P51 INTERFERON-INDUCED FATIGUE IN HEPATITIS C INFECTED PATIENTS IS ASSOCIATED WITH INCREASED EXPRESSION OF INDOLEAMINE 2,3-DIOXYGENASE IN PERIPHERAL BLOOD MONONUCLEAR CELLS

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Introduction Interferon-α (IFN)-based antiviral therapy for chronic hepatitis C virus (HCV) infection commonly induces fatigue and depression. IFN-induced symptoms may result from the activation of indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme, regulating the breakdown of tryptophan (Trp) into L-kynurenine (Kyn), expressed in immune cells and brain. IDO activation might result in Trp and serotonin depletion and accumulation of neurotoxic Kyn metabolites. IFN increases IDO gene expression in vitro and increased serum Kyn/Trp ratios have been reported in IFN-treated patients. However, a consistent relationship between Kyn/Trp and IFN-induced symptoms in HCV has not been shown.
Aim We sought to determine the relationship between IDO mRNA expression in PBMC, serum Kyn/Trp ratio and IFN-induced symptoms.
Method Fatigue Impact Scale (FIS) and Hospital Anxiety and Depression (HADS-D) questionnaires were completed by 19 patients at baseline and after 12 weeks treatment with PEGIFN-2a and ribavirin. Blood samples were taken from patients and 14 healthy controls. Total RNA was extracted from Ficoll separated PBMC and IDO mRNA was quantified relative to GAPDH using RT-PCR (Applied Biosystems). Expression at week 12 vs baseline was calculated as fold change using the $2^{-\Delta\Delta Ct}$-method. Serum Kyn/Trp was measured using HPLC/MS/MS.
Results IDO mRNA expression at baseline was similar in HCV patients and controls (ΔCt=9.76±0.39, ΔCt=9.73±0.28, p=NS). In the whole cohort, there was no change in IDO expression at week 12 vs baseline (ΔCt=10.0±0.23 vs ΔCt=9.76±0.39, p=NS), although serum Kyn/Trp increased significantly (p<0.001). However, patients with IFN-induced fatigue (ΔFIS>20; n=7) showed increased IDO mRNA expression (ΔΔCt= −0.97±0.58; median fold change =2.57) vs those without fatigue (ΔΔCt=0.96±0.53; mfc=0.89; p=0.02). Only modest increases in depression scores were seen (ΔHADS-D ≥5 in 5 patients) but no differences in ΔΔCt were seen compared to those with unchanged HADS-D. Baseline IDO mRNA expression was not predictive of IFN-induced fatigue or depression. There were no associations between baseline or week 12 Kyn/Trp ratios and IFN-induced fatigue or depression.
Conclusion We show for the first time that peripheral IDO gene expression in HCV patients is similar to healthy controls and IFN-treatment leads to differential induction of IDO mRNA. IFN-induced fatigue is significantly associated with increased peripheral IDO expression but not serum Kyn/Trp. Measurement of PBMC IDO mRNA may mirror CNS changes more accurately than peripheral Trp and Kyn levels. The modest prevalence of depression in this small cohort may explain the lack of association with depression.

P52 MACROPHAGE INFLAMMATORY PROTEIN-1 α/CC CHEMOKINE LIGAND 3 AND TUMOUR-ASSOCIATED MACROPHAGES IN HEPATITIS C VIRUS-RELATED HEPATOCELLULAR CARCINOMA: RELATION TO TUMOUR PROGRESSION AND ANGIOGENESIS

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Introduction Hepatitis C virus (HCV) is a major risk factor for development of hepatocellular carcinoma (HCC), however, the mechanism of hepatocarcinogenesis in HCV infection is still undefined. Chemokines, which can induce the migration of leucocytes and activate inflammatory/immune responses, have recently been implicated in the regulation of tumour growth.
Aim Therefore, the aim of the present work was to study the role of macrophage inflammatory protein-1 α/CC chemokine ligand 3 (MIP-1α/CCL3), a potent macrophage chemoattractant, in the

pathogenesis of HCV-related HCC in relation to tumour progression and angiogenesis.

Method 30 patients with HCV-related cirrhosis (15 patients with histologically-proven HCC and 15 patients without HCC) and 15 healthy subjects were enrolled in the study. The severity of liver disease was assessed according to Child-Pugh classification and the Model for End Stage Liver Disease (MELD) score. The tumour stage was classified using the Cancer of the Liver Italian Program (CLIP) scoring system. Histological tumour grading was performed according to the Edmondson and Steiner's criteria and the surrounding liver tissue was examined for assessing the modified histological activity index (HAI), presence of cirrhosis and the grade of steatosis. Expressions of MIP-1α/CCL3, CD68 [a marker for tumour-associated macrophages (TAM)] and CD105 (Endoglin) [for tumour angiogenesis and determination of microvessel density (MVD)] were studied in HCC and adjacent non-neoplastic liver tissues by immunohistochemistry. Serum MIP-1α/CCL3 levels were measured using solid phase sandwich enzyme linked immunosorbant assay kit. The sensitivity and specificity of serum levels of MIP-1α/CCL3 as markers for diagnosis of HCC have been assessed by plotting a receiver-operating characteristic (ROC) curve.

Results Patients with HCV-related HCCs showed significant increases in MIP-1α/CCL3 expression, $CD68^+$ TAM count and $CD105^+$ MVD in tumour tissues compared with adjacent non-neoplastic liver tissues ($p=0.0004$, $p<0.001$ and $p<0.001$ respectively). Serum MIP-1α/CCL3 levels were significantly higher in patients with and without HCC than in healthy subjects and in HCC patients than in patients without HCC ($p<0.001$). By plotting a ROC curve, the sensitivity and specificity of serum MIP-1α/CCL3 in discriminating cirrhotic patients with and without HCC were found to be 100% and 93.3% respectively at a cut-off value of 17.5 pg/ml. The MIP-1α/CCL3 expression in HCC tissues showed positive correlations with serum MIP-1α/CCL3 levels; tumour size, stage, histopathological grade; serum α-fetoprotein levels and $CD68^+$ TAM count and $CD105^+$ MVD in HCCs ($p<0.05$). Also, $CD68^+$ TAM count and $CD105^+$ MVD in HCC tissues were positively correlated ($p<0.001$). On the other hand, no correlations were found between MIP-1α/CCL3 expression, $CD68^+$ TAM count and $CD105^+$ MVD in HCCs on one hand and serum levels of aminotransferases, Child-Pugh score, MELD score and HAI and steatosis grade in the surrounding liver tissue ($p>0.05$).

Conclusion The CC chemokine, MIP-1α/CCL3, may play an important role in the pathogenesis and progression of HCC in HCV-related liver disease, possibly, through migration of macrophages to tumour microenvironment and enhancement of angiogenesis. MIP-1α/CCL3 may also serve as a potential serum biological marker and a useful therapeutic target for HCC.

P53 THE COST-EFFECTIVENESS OF HCV ANTIVIRAL TREATMENT FOR INJECTING DRUG USER POPULATIONS

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Introduction Injecting drug use is the main risk of HCV transmission in most developed countries. Hepatitis C virus antiviral treatment (peginterferon + ribavirin) is cost-effective for patients with no reinfection risk. Concerns about reinfection and non-compliance may discourage clinicians from treating injecting drug users (IDUs), despite the potential use of treatment as prevention in this population.

Aim Using a cost-utility analysis, we examined the cost-effectiveness of providing antiviral treatment for IDUs as compared to treating ex/non-IDUs or no treatment.

Method A dynamic model of hepatitis C transmission and disease progression among IDUs and ex-/non-IDUs was developed, incorporating: a fixed number of antiviral treatments allocated at the mild HCV stage over 10 years, no retreatment after initial treatment failure, and potential re-infection for cured IDUs. We performed a probabilistic cost-utility analysis estimating long-term costs and outcomes (measured in QALYs) and calculating the incremental cost-effectiveness ratio (ICER) to determine the cost-effectiveness of treating IDUs as compared to treating ex/non-IDUs or no treatment for three baseline IDU HCV prevalence scenarios (20%, 40%, and 60%).

Results Antiviral treatment of IDUs is the most cost-effective option in both the 20% and 40% baseline chronic prevalence settings, with ICERs as compared to no treatment (best supportive care) of £521 and £2539 per QALY saved, respectively. Treatment of ex/non-IDUs is dominated in these scenarios. At 60% baseline prevalence, treatment of ex/non-IDUs or IDUs is roughly equally cost-effective; treating ex/non-IDUs is more likely to be the most cost-effective option (with an ICER as compared to no treatment of £6803), and treating IDUs is dominated due to the high re-infection at this prevalence. A sensitivity analysis indicates that these rankings hold even when IDU SVR rates as compared to ex/non-IDUs are halved.

Conclusion Despite the possibility of re-infection, the model projections suggest that providing antiviral treatment to IDUs is the most cost-effective policy option in chronic prevalence scenarios <60%. Further research on how HCV treatment for injectors can be scaled up, and its impact on prevalence is warranted.

P54 CHASE-B (CHINESE HEPATITIS AWARENESS, SURVEILLANCE AND EDUCATION): A PILOT OF TARGETED CASE FINDING FOR HEPATITIS B VIRUS (HBV) IN THE BRITISH-CHINESE COMMUNITY

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Introduction Chronic HBV (cHBV) is a frequent cause of cirrhosis and liver cancer. Many infected individuals are unaware of their condition. Migrants from countries with high prevalence of cHBV, such as China and the Far East (seroprevalence 7–12%), are a high risk group for cHBV. Targeted HBV screening and vaccination is recommended by the AASLD[1] and the European Liver Patients Association (ELPA)[2] in high risk groups including subjects born in endemic areas. However, there are no current UK guidelines.

Aim To apply AASLD and ELPA recommendations to British-Chinese community of North East (NE) England.

Method Members of the NE Chinese community were invited to attend screening sessions at the Newcastle Chinese Healthy Living Centre [charity registration no. 1125227]. Dry blood spots were obtained by finger prick and tested for HBsAg and HBcAb (Abbott ARCHITECT). HBsAg positive individuals were advised to undergo confirmatory testing and be referred for specialist assessment.

Results 575 subjects were screened in 10 sessions (mean age 49±17 years, 61% female). 53 (9%) were HBsAg positive (48% female) indicating cHBV. 10 of these reported being previously diagnosed with HBV, but were not under follow-up. The prevalence of HBsAg positivity was 7.5% when previously diagnosed individuals