PM0-156 PLASMA HBSAG LEVELS CORRELATE WITH LIVER CCCDNA IN TOLERANT CHILDREN WITH INFANCY ACQUIRED CHRONIC HEPATITIS B INFECTION

doi:10.1136/gutjnl-2012-302514b.156

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Introduction Plasma HBsAg reflects the transcriptional activity of covalently closed circular (ccc) DNA within the liver rather than the absolute amount of cccDNA copies. Higher plasma HBsAg levels are reported among tolerant than immuno-active HBeAg positive chronic hepatitis B (CH-B) patients. Only limited information is available on the interaction of plasma HBsAg, expression of HBsAg and HBcAg within the liver and liver relaxed circular (RC) HBV DNA and cccDNA in patients with infancy-acquired CH-B.

Aims To evaluate whether there is a relationship between plasma HBsAg and HBV DNA levels and HBsAg/HBcAg expression within the liver and liver RC HBV DNA and cccDNA in tolerant children with infancy-acquired CH-B.

Patients 23 children (eight males, median age 10.2 yrs) with infancy-acquired CH-B (all HBeAg+) in tolerant stage underwent liver biopsy prior to antiviral therapy with lamivudine and interferon-α.

Methods Plasma HBsAg and HBV DNA levels were measured at therapy baseline by Abbott ARCHITECT® assay and real-time TaqMan PCR [both $\log_{10}$ IU/ml]. Baseline liver RC HBV DNA and cccDNA was quantified by real-time TaqMan PCR [copies/ng genomic DNA]. Immunostaining of formalin-fixed, paraffin-embedded liver specimens assessed HBsAg and HBcAg expression [# of positive cells per 1000 hepatocytes]. Results are presented as median, range.

Results Baseline plasma HBsAg levels were 4.67 (3.7–5.1), HBV DNA was 8.2 (7.1–8.9) both $\log_{10}$ IU/ml and ratio HBsAg/HBV DNA 0.57 (0.44–0.65). Liver RC HBV DNA was 4.41 (2–5.3) $\log_{10}$ copies/ng genomic DNA and cccDNA was 363 (0.3–3632) copies/ng genomic DNA. HBsAg is predominantly expressed in cytoplasm focally associated with membranous staining, 2.9 (0–56.9) positive cells/1000 hepatocytes, in contrast to HBcAg expressing predominantly in the nucleus, 8.3 (0.5–83.6) positive cells/1000 hepatocytes. There were positive bivariate Spearman correlations between plasma HBsAg levels and liver cccDNA (r=0.41, p=0.05), HBcAg liver expression and cccDNA (r=0.44, p=0.05), liver RC HBV DNA and cccDNA (r=0.67, p=0.04) and a trend towards correlation between plasma HBsAg and HBsAg liver expression (r=0.38, p=0.07).

Conclusion Plasma HBsAg levels correlate with liver cccDNA in tolerant children with infancy-acquired chronic hepatitis B infection suggesting that plasma HBsAg levels acts as a surrogate marker of cccDNA within the liver in tolerant patients.

Competing interests I Carey grant/research support from: BMS, Gilead, Y Zen: None declared, M Bruce: None declared, M Horner: None declared, S Bansal: None declared, D Vergani: None declared, G Mieli-Vergani: None declared.

PM0-157 HBSAG PLASMA LEVELS DECLINE HELPS TO PREDICT HBEAG LOSS BUT IS SIMILAR IN DIFFERENT NUCLEOS(T)IDE ANALOGUES REGIMENS

doi:10.1136/gutjnl-2012-302514b.157

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Introduction The kinetics of serum HBsAg (qHBsAg) decline predict response to treatment with pegylated interferon (Peg-IFN) in chronic hepatitis B (CH-B). Whereas nucleos(t)ide analogue (NA) therapy is associated with a sharp decrease in serum HBV DNA level due to inhibition of the viral polymerase, only limited data are available comparing the effect of different treatment regimens on qHBsAg kinetics. This study compared serum qHBsAg and HBV DNA kinetics in patients with CH-B receiving de-novo therapy with either tenofovir (TDF) 245 mg/day, entecavir (ETV) 0.5 mg/day or lamivudine 100 mg/day plus adefovir 10 mg/day (LAM+ADV).

Methods 205 CH-B therapy naïve monoinfected patients (75% males, 21% HBeAg positive, 21% cirrhotic, median age 36 years) were treated with TDF (n=50), ETV (n=62) or LAM+ADV (n=93) for at least 12 months. We quantified qHBsAg (Abbott ARCHITECT® assay) and HBV DNA (real-time TaqMan PCR) in serial serum samples at baseline, months 3 (M3), 6 (M6) and 12 (M12).

Results Median qHBsAg levels were similar at each time-point and were not influenced by treatment regimen. No patient achieved HBsAg loss. More patients receiving TDF achieved optimal virological response (VR), defined as HBV DNA <20 IU/ml), at M3 compared to ETV and LAM+ADV (60% vs 43% vs 40%, respectively; p=0.05) but not at M6 (76% vs 74% vs 79%) and M12 (80% vs 82% vs 82%). The proportion of patients achieving HBsAg decline >0.5 $\log_{10}$ IU/ml was higher in ETV cohort at M3 than in TDF and LAM+ADV (10% vs 2% and 2% respectively; p=0.05), but not at M6 (10% vs 6% vs 5%) and M12 (12% vs 10% vs 8%). HBeAg loss was more frequent in LAM+ADV and TDF groups than ETV (47% vs 33% vs 6%, respectively; p=0.03) and correlated with greater qHBsAg decline at all treatment time-points (M3: r=0.47, p=0.04; M6: r=0.55, p=0.03 & M12: r=0.58, p=0.03). Patients achieving VR had higher qHBsAg levels (M3: 3.71 vs 3.29 $\log_{10}$IU/ml; M6: 3.67 vs 3.24; and M12: 3.66 vs 3.24; all p<0.01), slower qHBsAg decline and fewer patients with qHBsAg >0.5 $\log_{10}$IU/ml from baseline compared to those with detectable HBV DNA.

Conclusion Serum qHBsAg kinetics during therapy were a good predictor of HBeAg loss. However, antiviral therapy in CH-B with nucleos(t)ide analogues in the first 12 months was similar between variable therapeutic approaches and there was no significant qHBsAg decline in contrast to HBV DNA suppression.

Competing interests M Horner: None declared, M Bruce: None declared, S Knighton: None declared, M Al-Freah: None declared, D Joshi: None declared, S Hughes: None declared, A Suddle: None declared, P Harrison: None declared, K Agarwal: None declared, I Carey grant/research support from: BMS, Gilead.

PM0-158 RS12979860 CC GENOTYPE IS ASSOCIATED WITH BASELINE HIGH NUMBERS OF CD56BRIGHT NK-CELLS, LOW NUMBERS OF CD3-CD56-CD16+ CELLS, LOW IL-10 HCV-SPECIFIC PRODUCTION IN CH-C THERAPY RESPONDERS

doi:10.1136/gutjnl-2012-302514b.158

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Introduction IL28B gene single nucleotide polymorphisms (SNPs) rs12979860 and rs8099917 help to predict treatment response in chronic hepatitis C (CH-C). Strong immune responses control HCV infection. Little is known on the association between IL28B SNPs, innate/adaptive immune responses in relation to Peg-IFN/ribavirin sustained virologic response (SVR) in CH-C.

Aims To evaluate the relationship between rs12979860 and rs8099917, pre-treatment frequency/phenotype of natural killer (NK) cells (innate immunity), HCV-specific immune responses (adaptive immunity), and SVR.

Patients 35 CH-C genotype 1 patients (23 males, median age 37 years) treated with Peg-IFN/ribavirin were divided in two groups: 18 responders (SVR), 17 non-SVR (nine non-responders and eight relapsers).
Methods rs12979860 and rs8099917 were tested by direct sequencing. Baseline numbers of NK cells ($CD3^-CD56^+$), their subsets $CD56^{dim}/CD56^{bright}$, $CD3^-CD56^{\pm}CD16^{\pm}$, and expression of NK cells activation/inhibition (NKG2D/NKG2A) markers were investigated by flowcytometry on peripheral blood mononuclear cells (PBMC). PBMC IFN-γ/IL-10 production after exposure to HCV antigens was evaluated by intracellular cytokine staining. Results are presented as medians.
Results Rs12979860 genotype CC was more frequent in SVR than non-SVR (85% vs 15%), while non-CC genotypes (CT/TT) were present in 32% SVR vs 68% non-SVR. 75% SVR had TT genotype for rs 8099917 vs 25% non-SVR and non-TT genotypes (GT/GG) were more frequent in non-SVR then SVR (80% vs 20%, all pbright subset was higher in SVR than non-SVR (6.4% vs 2.9%, p=0.03). $CD3^-CD56^-CD16^+$ cells subset was more frequent in non-SVR than SVR (11.4% vs 8.6%, p=0.05). The proportion of $CD56^{dim+}/NKG2D^+$ cells was higher in SVR than non-SVR (47.1% vs 36.3%, p=0.04). While number of CD4+ HCV core-specific IFN-γ producing cells was similar in all groups, the frequency of HCV core-specific CD4+ cells producing IL-10 was higher in non-SVR than SVR (4.3% vs 1.8%, p=0.05). Comparing patients according to rs12979860 CC vs no CC genotypes, CC genotype patients had more $CD56^{bright}$ cells (6.6% vs 3.1%, p=0.04), fewer $CD3^-CD56^-CD16^+$ NK cells (8.7% vs 11.1%, p=0.05) and fewer HCV-core specific $CD4^+/IL\text{-}10^+$ cells (1.9% vs 4.2%, p=0.05). There were no associations between rs8099917 genotypes TT vs no TT and innate or adaptive immune responses in this cohort.
Conclusion High numbers of $CD56^{bright}$ NK cells, low numbers of unconventional $CD3^-CD56^-CD16^+$ NK cells, and low HCV-specific IL-10 production at baseline are associated with IL28B gene SNP rs12979860 CC genotype and successful antiviral treatment of CH-C genotype 1.

Competing interests None declared.

PMO-159 ETHNIC ORIGIN AND VARIATION IN OUTCOME IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND HEPATITIS B INFECTION

doi:10.1136/gutjnl-2012-302514b.159

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Introduction Hepatocellular carcinoma (HCC) is a major cause cancer-related mortality, world wide. In particular, HCC is associated with chronic hepatitis B infection (CHB) in Africa and South East Asia. Most published data relating to the natural history of CHB and HCC originates from South East Asia; however due to differences in HBV genotype and potential environmental and genetic factors, it is not clear whether this data are applicable to the African population. Therefore, to explore this issue we have compared the characteristics and outcomes of patients with CHB and HCC according to ethnic origin.
Methods Patients with HCC complicating CHB, managed at King's College Hospital London, were identified from our clinic databases. Demographic information, laboratory parameters, initial tumour staging and outcome data, including HBe-antigen status, viral load and genotype, were collated where available. Comparison was performed between Black patients and patients of South East Asian origin.
Results In total, 295 patients with HCC and CHB were identified. Median age at the diagnosis of tumour was 37 years and 85% of patients were male. Ethnicity was classified as Black in 27% of patients and South East Asian in 21% of these patients. Cirrhosis was present in 81% whereas 8% were non-cirrhotic at diagnosis of HCC; data were unavailable in the remaining 11% of patients. 18% were HBe-antigen positive and 7% hepatitis C antibody positive. The distribution of HBV genotypes varied according to ethnic group, with genotypes A and E restricted to Black patients and genotypes B and C to South East Asian patients. On comparing these two groups, there were no differences in gender, the presence of cirrhosis, co-factors for liver disease, laboratory parameters or tumour stage, as assessed by the BCLC staging system. However, Black patients were significantly younger (median age: 44 vs 61 years, p<0.001). Although not significant, there was a trend towards a greater frequency of HBe-antigen positivity in the Black patients. No difference in viral load was observed. There was an increased probability of death within the follow-up period in the Black group (66% vs 39%, p=0.004). Comparison of Kaplan–Meier survival curves for the two groups demonstrated decreased survival following diagnosis of HCC in the Black group (log rank: p=0.31).
Conclusion In our cohort, we have observed that Black patients present at a younger age and have poorer length of survival in comparison to South East Asian patients. This may represent a more aggressive HCC phenotype that is associated with HBV genotypes A and E although there are potentially multiple confounding factors. Further research is required to determine the cause of this apparent inequality.

Competing interests None declared.

PMO-160 LIVER TRANSPLANTATION FOR CHRONIC HEPATITIS C IN NORTHERN IRELAND

doi:10.1136/gutjnl-2012-302514b.160

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Introduction Chronic hepatitis C (CHC) is a leading cause of chronic liver disease in the UK. Orthotopic liver transplantation (OLT) is commonly used for end stage cirrhosis or hepatocellular cancer secondary to CHC. Unfortunately recurrence of CHC in the graft of transplant recipients is almost universal, often leading to accelerated liver damage. Our aim was to assess the outcome of patients attending a Regional Liver Unit in Northern Ireland who underwent OLT for liver disease due to CHC.
Methods A retrospective study was carried out of patients from Northern Ireland who had OLT between 1998 and 2010 for CHC associated chronic liver disease. Cases were identified by review of the regional OLT database and cross-referenced with the centre where OLT was carried out (KCH, London).
Results Sixteen patients (11 male) underwent 20 OLTs for CHC between April 1998 and December 2010 (<10% of all OLTs). Mean age was 54 years. 13 patients had single OLT and 3 required multiple transplants. The HCV genotypes were 1 (7), 3 (5) and 2 (4). Prior to OLT, 10 patients received antiviral therapy—all failed (five non-responders, two relapsed following treatment and three failed to tolerate treatment). Data were only available on 19 OLT episodes. Immunosuppressant maintenance therapy was as follows: tacrolimus (9), tacrolimus + mycophenolate (4), cyclosporine (1) and mycophenolate + prednisolone (1). Short-term complications included acute cellular rejection in 5 (26.3%) requiring pulsed methylprednisolone (4) or IL2 blockade (1). Two patients developed