Results Intrahepatic vs peripheral blood NK cells demonstrated significantly less expression of CD16 (p NKG2D and NKp30 expression was increased in PBMCs of HCV patients with a more striking down regulation of NKG2D in the liver (p. There was no difference in NKp46 or NKG2A expression between the intrahepatic and peripheral NK cells in either cohort. However, the necroinflammatory score of HCV subjects correlated with NKp46 expression (p=0.003), CD107a expression (p=0.05) and IFN-γ (p=0.05). In the treated cohort, an increased rate of viral clearance correlated with an increased ability of the NK cells to upregulate CD107a (r^2=0.5 p<0.05) to increasing stimulation, which was inversely correlated with expression of NKp46 (r^2=0.85 p=0.001) at baseline.
Conclusion Intrahepatic NK cells acquire a distinct phenotype and functional profile. NK phenotype and function correlates with necroinflammatory score in HCV infection. The NK cells ability to be activated with IFNα is associated with rapid control of the virus.

Competing interests None declared.

PMO-175 CAN A 3-MONTH "STOPPING RULE" FOR PEGYLATED-INTERFERON-α BE APPLIED TO A UK POPULATION OF CHRONIC HEPATITIS B INFECTED PATIENTS OF MIXED GENOTYPE?

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Introduction Stopping rules have been proposed for the early discontinuation of Pegylated-Interferon-α (PEG-IFN-α) therapy in those patients who are considered unlikely to respond. Recent studies have shown that no reduction in quantitative HBsAg and the absence of >2 log decline in HBV DNA at 12 weeks therapy can predict non-response. However, these data are almost exclusively from genotype A and D cohorts. Here we test how robust this strategy would be in clinical practice and whether this rule could be applied to a UK population of diverse HBV genotypes.
Methods 49 patients (male=35) were treated with PEG-IFNα for CHB over the course of the study. Ten patients remain on therapy and eight patients discontinued due to poor compliance or intolerance. 31 patients (male=20), HBeAg positive (n=24), median age 31 (range 18–55) completed 48 weeks PEG-IFNα and were included in the analysis. HBV genotype was recorded for all patients (A=6, B=5, C=10, D=9, E=1). ALT, HBV DNA and HBsAg was quantified at baseline and longitudinally at 12-week intervals.
Results Of the 31 patients, 10 were considered responders; seven were HBeAg positive and seroconverted on therapy and three were HBeAg negative pre-therapy and considered responders with sustained immune control off treatment. The decline in HBV DNA and qHBsAg by 12 weeks was 3.99 log, 0.17 log (HBeAg positive group) and 2.9 log, 0.5 log (HBeAg negative group) respectively. 16/31 patients were non-genotype A or D. Of the responders from this group there was a decline in HBV DNA and qHBsAg of 4.10 log and 0.58 log respectively by 12 weeks. On sub-group analysis by genotype, there was no statistically significant difference in HBV DNA and qHBsAg decline at 12 weeks across all genotypes, when comparing HBV DNA and qHBsAg between genotype A and D and non A and D patients (p=0.40 and 1.0 respectively). More over adopting the rule of >2 log decline in HBV DNA and no decline in qHBsAg by 12 weeks, reveals we would not exclude those likely to respond; as all responders achieve the outlined viral response by 12 weeks therapy.
Conclusion These data highlight the utility of this stopping rule for PEG-IFNα across all genotypes. The absence of >2 log decline in HBV DNA and reduction in qHBsAg at 12 weeks therapy makes a favourable response unlikely. This rule should be adopted in clinical practice to avoid poorly tolerated side effects and the cost of completing 48 weeks therapy. Furthermore, this 12-week milestone would allow the early switch to an oral antiviral in PEG-IFNα non-responders.

Competing interests None declared.

PMO-176 INDUCTION MAINTENANCE TREATMENT IN CHRONIC HEPATITIS B; STEP-DOWN FROM TENOFOVIR AND LAMIVUDINE TO LAMIVUDINE MONOTHERAPY IS EFFECTIVE

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Introduction Tenofovir Disoproxil Fumarate (TDF) is a potent and effective oral antiviral used to treat Chronic Hepatitis B (CHB), but concerns remain about possible long-term toxicity and the costs of indefinite use. An induction-maintenance treatment strategy may allow the use of combination Lamivudine (LAM) and TDF, to avert the development of resistance, followed by maintenance of viral suppression with LAM. To date, there are no data on such a step-down strategy in HBeAg negative CHB. Here we report on patients in whom we safely discontinued TDF, while maintaining viral suppression and normal liver biochemistry.
Methods We selected patients who were had received combination therapy for a minimum of 18 months. Selection criteria included HBeAg negative disease, fibrosis score of <4/6 on biopsy, undetectable HBV DNA and normal serum ALT for a minimum of 12 consecutive months. Patients meeting these criteria were invited to stop TDF and step-down to maintenance LAM monotherapy. Patients were followed at monthly intervals to determine whether viral suppression and ALT normalisation was maintained in the absence of TDF.
Results 21 patients (13 male), median age 47, (range 39–62) discontinued TDF. Median follow-up was 3 months (range 1–10 months). During monthly follow-up biochemical and serological data have been measured. All patients had undetectable HBV DNA prior to step-down therapy to LAM and this remained undetectable during follow-up. Pre-discontinuation of TDF the median ALT was 27 (range 15–38) and during follow-up, on LAM monotherapy, was 22 (range 15–45), (p=NS). Median HBsAg level pre-discontinuation of TDF was log 3.48 (range 1.55–4.49) and 3.49 (range 1.55–4.55), (p=NS) on LAM monotherapy.
Conclusion We demonstrate no viral breakthroughs or biochemical flares on discontinuing TDF. These data suggest that an induction-maintenance strategy may be pursued in selected CHB patients to avoid long-term exposure to TDF and reduce the burden on healthcare budgets in the context of lifelong oral antiviral therapy.

Competing interests None declared.

PMO-177 MAXIMAL BOOSTING OF INNATE IMMUNITY DURING PEGYLATED INTERFERON-α THERAPY IS REACHED AT 48 WEEKS IN E-ANTIGEN POSITIVE CHRONIC HEPATITIS B

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Introduction Stopping-rules now exist for Pegylated Interferon-α (PEG-IFNα) treated Chronic Hepatitis B (CHB) patients. Despite the utility of such strategies, the immunological mechanisms that drive HBV DNA and HBsAg decline remain poorly understood. Recent data have identified changes in a subset of NK cells in HBeAg negative disease, which may determine treatment response. However, HBeAg positive disease responds more favourably to PEG-IFNα; here we report on a longitudinal analysis of changes in the immune profile in this cohort, to define the effects of PEG-IFNα on innate immunity.

Methods PBMCs from a cohort of 17 HBeAg positive patients followed longitudinally at 3 monthly intervals pre, during and post PEG-IFNα therapy were utilised. Phenotypic analysis of NK cells was performed by multicolour flow cytometry. Changes in the immune responses were correlated with simultaneous measurements of ALT, HBV DNA and quantitative HBsAg levels (Abbott ARCHITECT).

Results PEG-IFNα increased $CD56^{bright}$ NK cells by fourfold (mean fold change; MFC 3.7, p=0.0001). This was parallelled by the activation and proliferation of this subset, as marked by HLA-DR and Ki67 expression respectively (MFC 1.5 and 2.3, p=0.009 and p=0.0001 respectively). This increase was more marked at 48 weeks treatment, correlating with a nadir of HBV DNA and HBsAg. The activating (NKG2C and NKp30) and inhibitory (NKG2A) receptors were also analysed in this population. A twofold increase in NKp30 expression (MFC 2.27, p=0.04) was seen which was maximal at 48 weeks, while no significant change was noted for NKG2A and NKG2C. There was a twofold up-regulation of TRAIL expression on $CD56^{bright}$ NK cells, which temporally correlated with ALT levels, (MFC 1.8, p=0.0001), this effect was most dramatic at 24 weeks of therapy and sustained to 48 weeks.

Conclusion PEG-IFNα therapy in this cohort enhances and activates $CD56^{bright}$ NK cells. Similarly, TRAIL and NKp30 expression is augmented and sustained throughout treatment and all these effects are maximal at 48 weeks. The restorative innate immune changes begin early and increase throughout therapy in all patients. Thus, 48 weeks therapy may provide the optimal immunological conditions to introduce an oral-antiviral to achieve disease control in PEG-IFNα non-responders.

Competing interests None declared.

PM0-178 THE SIGNIFICANCE OF VIRAL AND SEROLOGICAL MARKERS IN PREDICTING LIVER DISEASE SEVERITY IN E-AG NEGATIVE HEPATITIS B VIRUS INFECTION

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Introduction In hepatitis B virus (HBV) infection, seroconversion to HBeAg negative/eAb positive accompanied by low serum HBV-DNA (persistently ≤2000 IU/ml) and low quantitative HBsAg (qHBsAg) signifies transition to an inactive carrier (IC) state. However, in patients with raised serum HBV DNA differentiating those with inactive disease (ID) from eAg negative chronic HBV (eAg-CHB) currently relies on liver biopsy. This study investigated whether serological (qHBsAg) and virological markers (serum HBV DNA) can predict disease severity in patients with eAg negative HBV across a range of HBV genotypes.

Methods Liver biopsy was performed in 364 consecutive eAg negative patients (median age 38 years, 212 males) who had HBV DNA >1000 IU/ml on at least two clinic visits over 6–18 months. ALT [IU/l], qHBsAg [Abbott ARCHTECT®], HBV genotype [direct sequencing] and HBV DNA [real-time TaqMan PCR] were evaluated at the time of liver biopsy.

Results Based on the liver histology findings, 217 had ID (an Ishak fibrosis score of F0-1) and 147 had eAg-CHB (≥F2). HBV genotype-E predominated (50%) followed by D (16%), A (15%), B (10%) and C (9%). Overall qHBsAg levels were higher in ID than eAg-CHB patients (median 3.84 vs 3.7 $\log_{10}$ IU/ml; p=0.02). Assessment by individual genotype demonstrated that qHBsAg levels remained higher in ID than eAg-CHB in genotypes A and E (4.01 vs 3.73 and 3.95 vs 3.8 $\log_{10}$ IU/ml; both p<0.05). However, in genotype B qHBsAg levels correlated with the severity of fibrosis [2.81 in F0-1 vs 3.34 in F≥2; p<0.01]. The qHBsAg levels were similar in ID and eAg-CHB in genotypes C and D. HBV genotype had no impact on the severity of liver fibrosis (p=0.16). Patients with eAg-CHB compared to those with ID had raised ALT [81% vs 65 %; p<0.01], higher HBV DNA (3.99 vs 3.6 $\log_{10}$ IU/ml; p<0.01), older age (39 vs 36 years; p<0.01) and more were males (68% vs 51%; p<0.01).

Conclusion In eAg negative patients with HBV DNA >1000 IU/ml, the relationship between qHBsAg levels and liver fibrosis was genotype specific. Even allowing for HBV genotype, the absolute qHBsAg level was a poor discriminator of clinically significant liver fibrosis.

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PM0-179 ROLE OF ANTIVIRALS IN ACUTE HEPATITIS B INFECTION; A 5-YEAR EXPERIENCE AT A LIVER TRANSPLANT CENTRE

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Introduction Acute hepatitis B in adults is successfully cleared in more than 95% of immunocompetent patients. A small proportion of patients develop fulminant hepatitis. Few controlled trials[1 2] have evaluated the role of antivirals in patients with acute severe hepatitis B (AS-HBV). The aim of this study was to report our experience of AS-HBV management at a tertiary centre.

Methods We retrospectively identified all patients between August 2006 and August 2011, referred to our centre with acute HBV infection (diagnosis based on recent onset of jaundice, detection of serum HBsAg and IgM HBcAb). 1-Year data following the diagnosis was collected using medical and electronic records. We identified all patients meeting at least one of the three criteria for AS-HBV[1] that is, INR ≥1.6, serum bilirubin ≥170 μmol/l and hepatic encephalopathy. Patients with other causes of acute liver injury such as alcohol and drugs were excluded.

Results 98 patients with acute HBV were identified during the study period. Of these, 64 (65.3%) patients had milder episodes. Thirty-four patients (34.7%; mean age 32, 50% females) had evidence of AS-HBV. Out of these, 17 (50%) patients had a bilirubin ≥170 μmol/l and 3 (8.8%) patients had INR ≥1.6 while 14 (41%) patients had both. None of the AS-HBV patients had evidence of encephlopathy. All patients had normal ultrasound scans of the liver and negative non-invasive liver screen, at the time of diagnosis. Of the 34 patients with AS-HBV, 20 (59%) patients received treatment with antiviral drugs, 55% with newer agents (Entecavir or Tenofovir) and 45% with older agents (Lamivudine or Adefovir). None of the patients developed any side effects to antiviral drugs. The remaining 14 (41%) patients with AS- HBV received supportive care