Results

Intrahepatic vs peripheral blood NK cells demonstrated significantly less expression of CD16 (p NK2G2 and NKp30 expression was increased in PBMCs of HCV patients with a more striking down regulation of NK2G2 in the liver. There was no difference in NKp46 or NK2A expression between the intrahepatic and peripheral NK cells in either cohort. However, the necroinflammatory score of HCV subjects correlated with NKp46 expression (p=0.005), 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 (r²=0.5; p<0.05) to increasing stimulation, which was inversely correlated with expression of NKp46 (r²=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 IFN-γ is associated with rapid control of the virus.

Competing interests

None declared.

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=29) completed 48 weeks peg-IFNα therapy 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-therapy and considered responders with sustained immune control off therapy. 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 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 (15 male), median age 47, (range 39–62) discontinued TDF. Median follow-up was 5 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 15–58) 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.
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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 5 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 CD56bright NK cells by fourfold (mean fold change; MFC 3.7, p=0.0001). This was paralleled by the activation and proliferation of this subset, as marked by HLA-DR and Ki67 expression respectively (MFC 1.5 and 2.3, p=0.0009 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 (NKGC2 and NKp30) and inhibitory (NKGA2A) 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 NKGC2.

There was a twofold up-regulation of TRAIL expression on CD56bright 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 CD56bright 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.

PMO-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 trials1,2 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-HBV1 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. Of these, 17 (50%) patients had a bilirubin > 170 μmol/l and 3 (8.3%) patients had INR > 1.6 while 14 (41%) patients had both. None of the AS-HBV patients had evidence of encephalopathy. All patients had normal ultrasound scans of the liver and negative non-invasive liver screen, at the time of diagnosis. Of the 54 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.