11 patients survived spontaneously (PALF-S) and nine died or required liver transplantation (PALF-NS). PALF-NS had higher peak INR (13.9 vs 7.4, p<0.001), SOFA score (13 vs 6, p<0.001), MELD (46 vs 35, p<0.05) and APACHE II score (20 vs 6.5, p<0.001). There were no differences in the total monocyte counts between PALF-NS and PALF-S (0.2 vs 0.43 X10 000 cells/dl). However, a significant reduction in the proportion of CD14lo/CD16hi MØ was observed in PALF-NS compared to PALF-S (0.5% vs 2.7%, p=0.01) and this was predictive of outcome (AUROC 0.838; values greater than 2% giving a sensitivity of 81%, specificity 89% for survival with medical management).

Conclusion These are the first reported data defining the relative proportions of MØ subsets in PALF. They show that the proportion of CD14lo/CD16hi MØ is significantly reduced in PALF, the degree of which is predictive for outcome. This reduction may be due to early sequestration of these MØ within the liver or other organs through CCR2 independent pathways.

OP23 BACTERIAL TRANSLOCATION AND REGULATORY T LYMPHOCYTES IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction Increased prevalence of bacterial infectious diseases has been observed in cirrhotic patients, classically attributed to immunosuppression-associated liver cirrhosis. Conversely, advanced states of liver cirrhosis predispose to increased antigenic load. A possible role has been ascribed to the translocation of bacteria and endotoxins (lypopolysaccharide, LPS) from the gut. LPS increases the plasma levels of LPS-binding protein (LBP), the principal plasma protein responsible for transporting LPS to immune effector cells. High serum LBP has been proposed to identify a subset of cirrhotic patients with ascitis characterised by an activation of the immune cells to producer proinflammatory cytokines. Moreover, raised levels of circulating LBP or proinflammatory cytokines have been implicated in the endothelial activation and haemodynamic derangement observed in cirrhosis. A chronic antigenic stimulus will induce a monocyte and lymphocyte activation.

Aim Intestinal permeability and bacterial translocation and their influence on T lymphocytes activation and differentiation in T reg were analysed in patients with compensated and decompensated liver cirrhosis. In particular, the regulation of T cell activation, mediated by co-stimulatory molecules, the expression of activation markers and the proportion of T CD4+ regulatory cells, as a function of bacterial translocation, were studied.

Method 40 patients with liver cirrhosis, 20 of them without previous decompensation (CC) and 20 with ascetic decompensation (DC), and 20 healthy controls (HC) were studied. Bacterial translocation was analysed by serum concentrations of lypopolysacharide-binding protein (LBP). Membrane expression of co-stimulatory molecules (CD28), activation markers (CD25 and CD122) and proportion of T regulatory cells (defined as those CD4+CD25highintracellular FoxP3+) were studied by flow cytometry with specific antibodies. Values of the variables were expressed as median (interquartile range). Comparisons between variables were made by the Mann–Whitney U test. Associations between variables were analysed by the Pearson's correlation coefficient.

Results Serum concentrations of LBP were significantly elevated in patients with compensated (7.7 (5.7–9.1 microg/ml) and decompensated (28.2 (10.7–40.6)) cirrhosis when compared with healthy controls (3.4 (2.7–4.2)) (p<0.001). Significantly higher concentrations of LBP were detected in those patients with higher portal hypertension. Those patients with decompensated cirrhosis shows an activation state characterised by increased percentages of CD25+ and CD122+ expression on CD4+ T cells. A decrease of CD28 expression was detected in T CD4+ lymphocytes from patients with decompensated cirrhosis (DC, 94% (89–98%); CC, 97% (92–98%); HC, 98 (96–99), DC vs HC: p=0.010). Moreover, T reg lymphocytes, expressed as a proportion of global T CD4+ cells, were significantly increased in patients with compensated and decompensated cirrhosis (DC, 14.7% (13.3–16.1%); CC, 10.3 (10.1–11.2); HC, 8.4 (7.2–8.7), p<0.001 in each case). A significant and positive correlation was detected between serum LBP concentration and percentage of CD4+ T reg (r=0.787, p<0.001).

Conclusion Patients with liver cirrhosis, fundamentally those with previous decompensation, shows increased intestinal permeability and chronic systemic antigenic stimuli. As a response to those, T lymphocyte activation is detected. Probably as a mean to decrease the continuous antigenic stimuli, a diminution of co-stimulation and an expansion of suppressor populations are observed in them.

Viral hepatitis

OP24 VASCULAR ENDOTHELIAL GROWTH FACTOR ACTIVATION OF LIVER SINUSOIDAL ENDOTHELIAL CELLS VIA VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 REGULATES HEPATOCELLULAR HEPATITIS C VIRUS REPLICATION

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Introduction Hepatitis C virus (HCV) is a major concern for human health, with an estimated 180 million people infected worldwide. HCV primarily infects hepatocytes in the liver and the majority of infected subjects develop progressive liver disease. Treatment options remain limited and hence, there is an urgent need for new therapies that target viral and host cell pathways. Vascular endothelial growth factor (VEGF) is a multifunctional cytokine that is produced by a variety of cell types in response to low oxygen and viral infections. VEGF targets vascular endothelial cells that are present in many tissues, including liver sinusoidal endothelial cells (LSEC). LSEC are in close apposition to hepatocytes in the liver and VEGF is known to regulate LSEC proliferation and function.

Aim We recently demonstrated that HCV promotes VEGF expression in hepatocytes (Mee et al, 2010 *Gastroenterology*) and the aim of this study was to investigate the role of VEGF in LSEC-hepatocyte interactions in HCV infection.

Method Using primary human LSEC we established direct LSEC-hepatocyte co-culture models to recapitulate the hepatic microenvironment. The effects of VEGF on LSEC and hepatocytes were analysed in both monoculture and co-culture.

Results Initial studies demonstrated that LSEC do not express the full complement of HCV receptors or entry factors and fail to support HCV replication. However, in vitro co-culture of LSEC and hepatocytes to model the hepatic epithelial-endothelial cell environment demonstrated that LSEC significantly reduce the permissivity of hepatocytes to support HCV replication. Interestingly, this effect was abrogated by inclusion of a neutralising antibody or a drug antagonist targeting VEGF receptor-2 (VEGFR-2). Importantly, recombinant VEGF had no effect on HCV replication in hepatocyte monocultures, suggesting that VEGF stimulates endothelial cells to modulate expression of molecules

that regulate hepatocyte permissivity to HCV infection. Indeed, conditioned media from VEGF treated LSEC significantly reduced the ability of hepatoma cells to support HCV replication, demonstrating that LSEC modulate expression of a soluble factor that reduces HCV infectivity in response to activation via VEGFR-2.

Conclusion In summary, these data demonstrate a new role for VEGF in endothelial-epithelial cell interactions in the liver that regulate HCV replication and highlight new areas for therapeutic intervention in chronic hepatitis C and other liver diseases.

OP25 CHRONIC HEPATITIS B VIRUS INFECTION IN THE UK: A MULTICENTRE STUDY OF CLINICAL AND VIROLOGICAL CHARACTERISTICS

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Introduction Hepatitis B virus (HBV) infection is an important health problem in the UK where 180 000 to 326 000 people are estimated to be chronic carriers of the virus and at increased risk of cirrhosis and hepatocellular carcinoma.

Aim To establish a national register of chronic HBV patients for long-term follow-up to provide comprehensive data on demographic, clinical, and virological characteristics of chronic HBV infection in the UK.

Method Adult patients with chronic HBV infection (HBsAg positive >6 months) under active follow-up in 15 UK liver centres were eligible. Patient recruitment commenced in February 2007. Demographic and clinical data were recorded for all patients. Serum samples were collected on a subset of patients to determine HBV genotype and presence of mutations by sequencing.

Results 1147 patients have been registered. Their mean age was 43±13 years; 57% were male. The most common ethnicities were Chinese (26%), white (22%) and Pakistani (18%). The majority (81%, 676/831) were born outside the UK primarily in Pakistan (15%), Hong Kong (12%) and China (10%). 22% were HBeAg positive. Cirrhosis was present in 17% of cases that had a liver biopsy (n=447). 63% were HBV antiviral treatment naïve. 33% were currently on treatment of which 53% were on monotherapy primarily with either lamivudine (53%) or entecavir (28%). HBV DNA was currently undetectable in 53% (193/362) of treated subjects. The prevalence of HBV genotypes in those sequenced (n=293) was as follows: A (14%), B (17%), C (18%), D (42.7%), E (8%) and G (0.3%). HBV genotypes differed according to ethnicity ($p<0.001$): whites were predominantly genotypes A (46%) and D (46%), Chinese genotypes B (44%) and C (46%), black Africans genotypes A (21%) and E (53%) and Pakistanis genotype D (97%). Precore and basal core promoter region mutations (BCP; T1762/A1764) occurred in 45% (127/280) and 15% (42/280) of those tested, respectively. 20% (56/280) of the samples carried both precore and BCP mutations. HBsAg mutations indicative of altered antigenicity and could potentially be involved in vaccine escape were detected in 19% (54/286). Polymerase mutations associated with antiviral resistance were identified in 23% (18/77) (only those currently/previously on treatment).

Conclusion We have established the first nationwide chronic HBV register in the UK. In our study population, chronic HBV infection was predominant in immigrants born in countries with high HBV prevalence. A strong association was found between HBV genotypes and ethnicity. Precore mutations were more common than BCP mutations and one-fifth of those tested carried both mutations.

The cross-sectional data have enabled exploration of epidemiological associations with chronic HBV infection, the use of antivirals, molecular typing and emergence of novel resistance strains in clinical practice which may differ from clinical trial results. Prospective follow-up of the cohort will allow further characterisation of long-term outcomes.

Transplant

OP26 PREDICTING THROMBOTIC COMPLICATIONS AFTER LIVER TRANSPLANTATION IN PATIENTS WITH BUDD CHIARI SYNDROME

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Introduction Myeloproliferative disorders (MPD) are the commonest cause of Budd Chiari syndrome (BCS). A somatic mutation of the tyrosine kinase JAK2 gene (JAK2V617F) is present in a large proportion of patients with MPD and is used as a screening tool to detect occult MPD. Recently a germline 46/1 haplotype block and mutations in the TET2 gene have also been implicated in the pathogenesis of MPD. We evaluate whether these underlying genetic abnormalities are relevant to the occurrence of thrombotic complications post liver transplantation (LT).

Method Samples of DNA were extracted from total blood or bone marrow. Real-time PCR was performed to screen for JAK2 mutations. TET2 mutations were analysed by next generation high throughput DNA sequencing (Roche 454). DNA was analysed by pyrosequencing for two SNP's which tag the 46/1 haplotype. Histology of liver biopsies performed for graft dysfunction were reviewed for evidence of veno-occlusive disease (VOD). The INR post LT and patient outcomes were recorded.

Results 36 patients underwent LT for BCS between 1995 and 2008. Median duration of follow-up after LT was 40 months (1–195 months) and 1-year survival was 84%. Pro-coagulant conditions were identified in 22 patients (MPD n=17, Protein C Deficiency n=2, Behcet's n=2 and lupus anti-coagulant n=1). The remaining 14 patients were classed as idiopathic. Overall, 22/36 (61%) were positive for the JAK2 mutation, 6/27 (22%) for the TET2 mutation and 19/26 (73%) for the 46/1 haplotype. In the idiopathic cohort, 8/13 (63%) tested positive for JAK2 suggesting latent MPD. All patients were treated with warfarin following LT. Thrombotic complications occurred in 12/36 (33%) and included hepatic artery thrombosis (n=3, 2/3 being late), VOD (n=7), splenic vein thrombosis (n=1) and portal vein thrombosis (n=1), at a median time of 40 months post LT (range 1–164 months). Re-transplantation was more common in those with thrombotic complications (7/12 (58%) vs 1/24 (4%), (p=0.0006)) and mortality was higher (4/12, (25%) vs 3/24, (13%)), but this did not reach statistical significance (p=0.2). The presence of a JAK2 mutation was associated with the development of a thrombotic complication post LT (11/12 vs 1/24, p=0.01). Neither the 46/1 haplotype nor the TET2 mutation was associated with an increase in post LT thrombotic complications or morbidity. Mean INR was not significantly different in those patients who developed a thrombotic complication (2.73 vs 2.70, p=NS).

Conclusion A JAK2 mutation appears to be associated with an increased risk of recurrent BCS and other thrombotic complications post LT. Thrombotic complications following LT are associated with an increase in morbidity and mortality. In patients with a JAK2 mutation, the role of additional anticoagulation or JAK2 inhibitor therapy needs to be investigated to try and prevent thrombotic complications.