not systemic pressure, compared to placebo which had minimal effect on either parameter.
Conclusion We demonstrate for the first time that H2-RLN will effectively downregulate MFB contractile filament expression, contractile function and has a portal hypotensive effect in vivo. Our findings support the deployment of H2-RLN in clinical studies of cirrhosis and PHT.

Viral hepatitis

OP11 FINAL RESULTS FROM TELAPREVIR PHASE II STUDIES IN GENOTYPE 1 TREATMENT-NAIVE OR EXPERIENCED SUBJECTS WITH CHRONIC HEPATITIS C

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Introduction Current standard of care (SOC) for treatment of HCV Genotype 1 (G1) naive patients comprises of pegylated interferon (P) plus ribavirin (R) for 48 weeks resulting in a sustained viral response (SVR) of 42 to 46% in treated patients. Telaprevir (TVR) is a novel selective inhibitor of the HCV NS3-4A protease. We report here results from phase II program.
Method PROVE 1 (n=263) and PROVE 2 (n=334) were randomised controlled phase IIb comparisons of 12 weeks TVR plus PR up to 48 weeks vs PR alone in G1 treatment-naïve patients. In the same population, the C208 study (n=161) compared TVR dosed every 8 h or every 12 h in combination with P2a or P2b with a response guided therapy design. In treatment experienced patients, the PROVE 3 trial (n=453) compared different TVR-based regimens to PR.
Results Higher SVRs compared to SOC in treatment-naive subjects were observed in the TVR groups (61–69%) in the PROVE 1 and 2 studies as well as the C208 study (81–85%). In PROVE 3, 51% (vs. 14% in control) of previous non-responders achieved SVR. The most common AEs through week 48 included; pruritus, rash, anemia, fatigue, weakness and headaches. Overall discontinuation of all drugs due to rash was observed in 4–7% of the subjects.
Conclusion TVR-based triple therapy significantly improves SVR rates in comparison to SOC in G1 HCV infected patients. It offers the potential to reduce treatment duration by half in the majority of treatment-naive patients. Phase III studies of TVR-based regimen are currently underway.

OP12 UK EXPERIENCE OF TREATMENT OF CHRONIC VIRAL HEPATITIS C IN CHILDREN AND ADOLESCENTS: PREDICTORS OF VIRAL RESPONSE AND QUALITY OF LIFE

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Aim The aim of this study was to review efficacy, tolerability and quality of life (QoL) in children with chronic hepatitis C (HCV) treated with pegylated interferon (PEG-IFN) alfa2a and ribavirin in 3national specialised referral centres in the UK.
Method Demographic, laboratory and clinical outcome data on children up to 18 years of age treated for HCV with PEG-IFN alfa2a and ribavirin were reviewed. Information gathered from QoL questionnaires (CHQ-PF28) completed by parents during their children's treatment was also available for one of the centres. Sustained viral response (SVR) was defined as undetectable HCV RNA at 24 weeks following end of treatment.
Results The study sample comprised 75 children of whom 38 were males. The median age at the start of the treatment was 10 years (3.0–17.2 years). The most common mode of infection (83%) was via maternal transmission. Thirty-four patients were Genotype 1 (G1); 39 Genotype 2&3 (G2&3); 2 Genotype 4 (G4). SVR was achieved in 47 (73.4%); 53% G 1; 90% G 2&3; 100% G 4. There was no significant difference between baseline ALT and/or AST levels in those who achieved SVR compared to the non-responder group. However the first group had at least 30% lower ALT and /or AST levels at 24 weeks post-treatment compared to the latter group p=0.003 and p=0.001, respectively. Children starting treatment <5 years of age had higher SVR compared to older age groups, however this was not statistically significant p=0.7. Low viral load at the start of the treatment (<500 000 IU/mL) did not have significant effect on viral response p=0.5. Early viral response (EVR) at 12 weeks of treatment was achieved in 46 and sustained in 40/46 (87%). Data on rapid viral response (RVR) at 4 weeks of treatment were available in 25; 17/25 (68%) achieved response which was sustained in 16 (94%). There was no significant change in the z scores for weight and height from start of treatment compared to 24 weeks post treatment follow-up (p 0.2 and 0.5, respectively). Data on QoL were available for 31/75 children and their families. At 12 weeks of treatment the child's general health was perceived to be poorer with limitation of physical activity and higher frequency of pain compared to other stages of treatment with values returning to baseline at the end of treatment and at follow up. There were no serious side effects reported and none discontinued treatment due to side effects.
Conclusion HCV treatment with PEG-IFN and ribavirin is well tolerated by children with minimal negative impact on the quality of life of a cohort of the studied children and no significant effect on growth. EVR and RVR are good predictors of treatment response.

OP13 SPONTANEOUS RESOLUTION OF ACUTE HEPATITIS C VIRUS INFECTION CORRELATES WITH THE RECONSTITUTION OF THE CIRCULATING CD56DIM NATURAL KILLER-CELL POOL

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Introduction Efforts to identify the immune-correlates responsible for resolution of hepatitis C virus (HCV) infection are fundamental to develop new treatment strategies and an effective vaccine against HCV. We have previously shown that imbalanced natural killer (NK)-cell subsets, with hyper-expression of co-inhibitory markers, are associated with chronic HCV infection.
Aim In this study we aim to assess the role of NK-cells in determining the outcome of acute HCV infection in a cohort of well characterised patients.
Method We analysed 12 patients with acute HCV infection who met the following criteria: ALT>10xULN, exposure to HCV within previous 4 months and HCV-RNA(+). Viral load was determined by qPCR. Peripheral blood mononuclear cells collected at 3 time-points (baseline, BL; month 1, M1; month 6, M6) were stained with fluorochrome-labelled antibodies to NK-cells (CD3/CD56/CD16). Proportions of CD56dim(CD16bright) and CD56bright(CD16dim) subsets and expression of PD-1/PD-L1 were evaluated by 6-colour flow cytometry and correlated with HCV-RNA and ALT at each time-point and over-time. Supernatants from cell-cultures in the presence of HCV-antigens were collected for cytokine analysis and quantification.

Results Six patients resolved HCV spontaneously (Resolvers), whilst six developed chronic infection (Chronics). At presentation, mean viraemia and ALT levels did not differ between Resolved and Chronic patients. In Resolvers HCV-RNA became undetectable at M3, which was then followed by ALT normalisation. Overall, Resolvers had higher proportions of total NKs than Chronics (p=0.023). Cytotoxic CD56dim NK cells were also higher in Resolvers (p=0.001), and became progressively predominant within their total NK pool, as shown by their progressive increase of the CD56dim/CD56bright ratio, which differentiated Resolvers from Chronics after M1 (p=0.01). In Chronic patients' cytotoxic CD56dim NK cells had, however, an overall greater expression of the cytotoxicity marker CD16 (p=0.008). Chronic patients also had higher proportions of both subsets of NK cells expressing the immunoinhibitory marker PD-1 (p=0.02), and stronger per-cell expression of the immunoinhibitory ligand PD-L1 on CD56dim NK cells (p=0.001). Analysis of clinical parameters revealed that in Resolvers the progressive increase of CD56dim/CD56bright ratio correlated with the decline of HCV-RNA over-time (r=−0.997, p=0.042), due to reduction of CD56bright (r=0.999, p=0.011) and expansion of CD56dim (r=−0.997, p=0.041). At M1, Resolvers' CD56dim were positively correlated with ALT (r=0.820, p=0.046).

Conclusion In patients with acute HCV infection the proportions and evolution of the two functionally distinct NK cell subsets differ in patients that resolve the infection compared to those who become chronically infected. A favourable outcome of infection is associated with the establishment of a defined NK profile, with predominance of CD56dim (cytotoxic) NK cells with low expression of the immunoinhibitory markers PD-1 and PD-L1, which may be linked to an improved early clearance of virus-infected hepatocytes, as shown by the correlation of this subset with serum HCV-RNA and ALT decline.

OP14 MEASUREMENT OF LOW DENSITY APOLIPOPROTEIN B ASSOCIATED HEPATITIS C VIRUS LIPOVIRAL PARTICLES IN GENOTYPE 1 INFECTION IS MORE CLINICALLY RELEVANT THAN TOTAL VIRAL LOAD

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Introduction The density of hepatitis C virus (HCV) in plasma is heterogeneous but the factors that influence this are poorly understood. Evidence from animal models and cell culture suggest that low-density apolipoprotein B (apoB)-associated HCV lipoviral particles (LVP) are more infectious than high density HCV.

Aim We measured HCV LVP in patients with chronic hepatitis C genotype 1 (CHC-G1) and examined metabolic determinants of LVP load and clinical correlates.

Method Fasting lipid profiles and HOMA-IR (homeostasis model assessment of insulin resistance) were determined in 51 CHC-G1 patients. LVP and non-LVP viral load were quantitated by real-time RT-PCR of plasma at density d<1.07 g/ml and d>1.07 g/ml, respectively, following iodixanol density gradient ultra-centrifugation. The LVP ratio was calculated using: LVP/(LVP+non-LVP)=LVP ratio.

Results The mean LVP ratio was 0.241 but varied 25-fold (0.029 to 0.74). When divided above and below the median value of 0.177, those with high LVP ratio had metabolic syndrome characteristics, higher liver stiffness and poorer early virological response rates (EVR) (see Abstract OP14 table 1).

Abstract OP14 Table 1 High vs low HCV LVP ratio—clinical and metabolic characteristics

	Low LVP ratio (n=25)	High LVP ratio (n=26)	p-value
Waist circum (cm)	85.7±11.1	92.7±12.2	0.037
Liver Stiffness (KPa)	9.53	19.54	0.001
Triglycerides mmol/l	1.08±0.46	1.62±0.15	0.015
HDL cholesterol mmol/l	1.36±0.33	1.11±0.25	0.015
TG/HDL ratio	0.84±0.4	1.62±1.1	0.003
HOMA IR	1.25±0.68	2.17±1.3	0.008
EVR (%)	31%	26%	0.037

Univariate analysis showed LVP ratio correlated with HOMA-IR (p=.004) and triglyceride (TG)/HDL-C ratio (p=0.004), but not with apoB. In multivariate analysis HOMA-IR was the main determinant of LVP load (log10 IU/ml) (p=0.037; R2=16.6%) but TG/HDL-C ratio was the strongest predictor of LVP ratio (p=0.019; R2=24.4%). Higher LVP ratios were associated with non-response to antiviral therapy (p=0.037) and with greater liver stiffness (p=0.001). There was no association between total viral load and host clinical and metabolic parameters.

Conclusion Measurement of HCV LVP is of more direct clinical relevance than total HCV viral load. Insulin resistance and associated dyslipidaemia are the major determinants of low-density apoB-associated LVP in fasting plasma. This provides a novel mechanism to explain why insulin resistance is associated with more rapidly progressive liver disease and poorer treatment outcomes.

Transplant

OP15 EARLY BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION: INCIDENCE, RISK FACTORS AND CENTRE EFFECT

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Introduction Although biliary disease is one of the most common complications of liver transplantation, its incidence and risk factors have not been previously determined in a large risk-adjusted analysis.

Method Using the United Kingdom and Ireland Liver Transplant Database, we sought to identify the incidence of and independent risk factors for early biliary complications (EBC, defined as the occurrence of a biliary tract leak, or stricture either of which required endoscopic, percutaneous or surgical intervention or culminated in graft loss within the first 3 months after transplantation) among 7044 adult, orthotopic, single-organ liver transplants between March 1994 and February 2007. Univariate and multivariable logistic regression models were fitted to examine the association between EBC and a wide range of recipient, donor and graft risk factors.

Results The incidence of EBC in the cohort was 8.5%, of which 5.2% were strictures and 4.7% were bile leaks. Multivariable analysis identified the following independent risk factors for EBC: lower donor-recipient age difference (per year, OR 0.99 p<0.003), lower pre-transplant serum albumin (per g/dL, OR 0.84 p<0.009), higher pre-transplant serum bilirubin (per mg/dl, OR 1.01 p<0.008), longer cold ischaemia time (per hour, OR 1.04 p=0.01), negative donor rhesus antigen (OR 1.39 p<0.003), higher donor haemoglobin (per g/dl, OR 1.05 p<0.03), presence of donor urinary tract infection (OR 2.63 p<0.04), use of live (vs brain-dead) donors (OR 5.89 p<0.005) and utilisation of biliary stent vs duct-to-duct reconstruction (OR 2.22 p<0.03). In addition, 5 of the 8 transplant centres in the UK and Ireland experienced a significantly higher adjusted risk of EBC compared to the centre with the lowest incidence, the ORs ranging between 1.48 (p<0.02) and 3.76 (p<0.001).

Conclusion This multi-centre analysis, the largest reported to date, has identified several novel recipient, donor and graft risk factors that could be utilised to stratify the risk of EBC among patients