chronic hepatitis C (CH-C). Control of HCV infection is linked to strong immune responses. Little is known on the association between IL28B SNPs, innate and adaptive immune responses in relation to therapy outcome in CH-C.

Aim 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 Peg-IFN/ribavirin response.

Method Patients: 19 CH-C genotype 1 patients (13 males, median age 47 years) treated with Peg-IFN/ribavirin were divided in 3 groups: 10 responders (SVR), 5 non-responders (NR) and 4 relapsers (Rel).

Methods: rs12979860 and rs8099917 were tested by direct sequencing. Baseline numbers of NK cells (CD3⁺CD56⁺), their subsets CD56^{dim}/CD56^{bright}, CD3⁺CD56⁺CD16⁺ and expression of NK cell activation/inhibition (NKG2D/NKG2A) markers were investigated by flowcytometry on peripheral blood mononuclear cells (PBMC). PBMC IFN- γ and IL-10 production after exposure to HCV-core, NS3, NS4, NS5 antigens was evaluated by intracellular cytokine staining. Results are presented as medians.

Results rs12979860 haplotype CC was present in 32% of patients (40% SVR and 50% Rel), CT in 63% (60% SVR, 50% Rel and 80% NR) and TT in 5% (20% NR); rs8099917 haplotype TT was present in 68% (80% SVR, 75% Rel and 40% NR) and GT in 32% (20% SVR, 25% Rel and 60% NR). Baseline number of NK cells was similar in all groups, but that of CD56^{bright} cells was higher in SVR than Rel/NR (6.7% vs 3.3%, $p=0.04$). CD3⁺CD56⁺CD16⁺ cells were more frequent in NR and Rel than SVR (14.4% vs 10.1% and 7.7%, $p=0.05$). The proportion of CD56^{dim} cells NKG2D⁺ was higher in SVR than Rel and NR (51.1% vs 37.3% and 25.2%, $p=0.04$). While number of HCV-specific IFN- γ producing cells was similar in all groups, IL-10 producing cells were higher in Rel and NR than SVR for HCV core (CD4⁺/IL-10: 4.8% vs 3.5% vs 1.8%, $p=0.05$). Compared to patients with rs12979860 CT/TT haplotypes, those with CC haplotype had more CD56^{bright} cells (6.8% vs 3.5%, $p=0.04$), but fewer CD3⁺CD56⁺CD16⁺ NK cells (7.9% vs 14.2%, $p=0.05$) and HCV-core specific CD4⁺/IL-10⁺ cells (4.5% vs 2.1%, $p=0.05$). There was no association between rs8099917 haplotypes, NK-cell number/phenotype and HCV-specific immune responses.

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 haplotype and successful antiviral treatment of CH-C genotype 1.

P58 GENETIC, VIROLOGICAL AND IMMUNOLOGICAL PRE-TREATMENT PREDICTORS OF THERAPY RESPONSE TO PEG-IFN/RIBAVIRIN IN CHILDREN WITH CHRONIC HEPATITIS C

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Introduction Vertically acquired chronic hepatitis C (CH-C) is a mild disease in childhood but may accelerate in adolescence. Effective early therapy with pegylated interferon (Peg-IFN) and ribavirin (Riba) prevents progressive liver damage. Control of HCV infection depends on both innate and adaptive immunity. Little is known about treatment predictors in children with CH-C.

Aim To assess whether single nucleotide polymorphisms (SNP) near IL28B gene rs12979860 and rs8099917, HCV genotype (G) and pre-treatment innate and adaptive immunity [frequency/phenotype of

natural killer (NK) cells, HCV-specific T cell responses, frequency/phenotype of T regulatory cells (T-regs), plasma levels of IFN- γ inducible protein 10 (IP-10)] predict therapy response in children with CH-C.

Method Patients: 32 children with CH-C (19 males, median age 12 yrs, 53% G1) treated according to genotype with Peg-IFN (60 μ g/m²/week) and riba (15 mg/kg/d) were divided into responders (22, R), relapsers (4, Rel) and non-responders (6, NR).

Methods: rs12979860 and rs8099917 were tested by direct sequencing; baseline numbers of NK cells (CD3⁺CD56⁺) and their subsets CD56^{dim}/CD56^{bright}, CD3⁺CD56⁺CD16⁺, of CD4⁺ cells expressing programmed death receptor (CD4⁺PD1⁺) and of T-regs (CD4⁺CD25⁺FoxP3⁺) by flowcytometry on peripheral blood mononuclear cells (PBMC). PBMC IFN- γ and IL-10 production after exposure to HCV-core, NS3, NS4, NS5 antigens was evaluated by intracellular cytokine staining. Baseline IP-10 plasma levels [pg/ml] were measured by ELISA. All presented as median.

Results rs12979860 haplotype CC was present in 34% (91% R and 9% NR), CT in 47% (73% R, 7% Rel and 20% NR) and TT in 19% (17% R, 50% Rel and 33% NR); rs8099917 haplotype TT was seen in 50% (88% R and 12% NR), GT in 44% (50% R, 29% Rel and 21% NR) and GG in 6% (50% R and 50% NR) patients. Non-G1 CH-C was linked with better response than G1 (53% vs 80%, $p=0.02$). Baseline number of CD56^{bright} NK cells was higher in R than Rel & NR (3.7% vs 1.8% and 1.3%, $p=0.05$). Compared to R, Rel and NR had higher numbers of CD3⁺CD56⁺CD16⁺ cells (17.4% vs 12.9% & 10.7%, $p=0.05$), of HCV-core-specific IL-10 producing cells (CD4⁺/IL-10: 4.4% and 3.8% vs 1.7%, $p=0.03$), of CD4⁺PD1⁺ cells (7.1% and 6.9% vs 4.3%, $p=0.03$) and of T-regs (4.2% and 3.0% vs 1.4%, $p=0.04$). Baseline plasma IP-10 levels were higher in NR than Rel and R (85 vs 34 and 15, $p<0.01$). By multivariate analysis only possession of CC rs12979860 and TT rs8099917 haplotypes and low baseline IP-10 levels were associated with response to therapy.

Conclusion Possession of both major haplotypes CC rs12979860 and TT rs8099917 for IL28B gene SNPs and low baseline IP-10 levels predict successful therapy response in children with CH-C.

P59 SUBANALYSES OF THE TELAPREVIR LEAD-IN ARM IN THE REALIZE STUDY: RESPONSE AT WEEK 4 IS NOT A SUBSTITUTE FOR PRIOR NULL RESPONSE CATEGORISATION

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Introduction On treatment, a poor therapeutic response to peginterferon (P)/ribavirin (R) is defined as a <1 log₁₀ decline in viral load at week 4. Null response (NR) to a current or prior course of PR is defined as a <2 log₁₀ decline in HCV RNA at week 12. The FDA adopted the week 12 NR definition in its recent draft guidance. The REALIZE study uniquely enrolled classically defined prior NR, partial responders and relapsers, and included an arm with a PR lead-in (L-I) phase. This design allows a comparison of on treatment response after 4 weeks of PR with prior response categories, including a comparison of 'null response', as well as the relationship between $<$ or -1 log₁₀ RNA decline and SVR in response to T/PR treatment.

Method Patients in the lead-in arm (N=240) received 4 weeks of PR followed by telaprevir (T) 750 mg 8 hourly for 12 weeks combined with PR followed by 32 weeks of PR alone. Control patients (N=121) received 48 weeks of PR. All patients received pegylated interferon alfa-2a.

Results 10% of prior relapsers and 31–40% of partial responders (shaded cells), had <1 log₁₀ decline in HCV RNA at week 4 in the control and L-I arm, respectively. SVR rates in the T L-I arm among prior relapsers and partial responders were higher (62% and 56%, respectively; combined SVR=58%) than in prior week 12 NR who experienced <1 log₁₀ decline in HCV RNA (15%). Although patients with -1 log₁₀ response at end of the L-I phase had the highest SVR rates, SVR in T/PR patients with <1 log₁₀ was considerably higher ($62 \pm 15\%$) than control (0%).

Conclusion Poor interferon responders on treatment (<1 log₁₀ decline in HCV RNA at week 4) are not the same as prior PR NR (<2 log₁₀ at week 12). SVR rates in T/PR patients were higher than control irrespective of their response ($<$ or -1 log₁₀) at the end of the L-I phase. Safety findings in the T arm were similar irrespective of week 4 response.

P60 PRE-TREATMENT IP-10 CONCENTRATIONS ARE ASSOCIATED WITH A SUSTAINED VIROLOGICAL RESPONSE IN HIV/HCV CO-INFECTED PATIENTS

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Introduction Treatment of chronic HCV (cHCV) in HIV positive patients with pegylated interferon (PEG-IFN) and ribavirin (RIB) is associated with poorer treatment outcomes and an increased side effect profile. Strong immune T helper type 1 responses towards HCV determine outcome of infection. Interferon γ inducible protein 10 (IP-10) has been shown to correlate with treatment response in cHCV mono-infection but limited data are available for HIV co-infected patients.

Aim To investigate whether pre-treatment plasma levels of cytokines/chemokines differ between HIV/HCV co-infected and HCV mono-infected patients and whether they can predict response to PEG-IFN and RIB therapy.

Method Pre-treatment plasma samples were studied in HIV positive patients co-infected with cHCV and HIV negative cHCV patients. Plasma levels of IFN- γ , interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10 and IP-10 (all pg/ml) were measured by ELISA. Patients were matched according to genotype, fibrosis stage and age. All patients were treated with PEG-IFN α 2a and weight based RIB for 24 weeks or 48 weeks according to genotype. All patients were previously treatment naive. Virological response was divided into SVR, non-response (NR) and responder relapse (RR). All results are presented as medians.

Results 37 HIV positive patients (CD4 count 495 cells/ml, undetectable HIV viral load in 86%) co-infected with HCV ([HCV viral load (VL) 1.68E6 IU/ml, 54% genotype 1, 7 (19%) patients with advanced fibrosis on biopsy (Ishak F >5)] were divided according to virological response [n=23 SVR (62%), n=7 RR, n=7 NR]. 35 HIV negative patients with cHCV [HCV VL 2.12E6, 64% genotype 1, 5 (14%) patients with advanced fibrosis (Ishak F >5)] were also divided according to virological response [n=23 SVR (66%), n=7 RR, n=6 NR]. Irrespective of HIV status, IP-10 (62 vs 105, $p=0.006$) and IL-6 (4 vs 7, $p=0.03$) levels were lower at baseline in patients who achieved an SVR. Baseline IP-10 (92 vs 49, $p=0.009$) and IL-8 (39 vs 22, $p=0.01$) were higher in the HIV positive group but the concentrations of IFN- γ , IL-2, IL-4, IL-6, IL-10 were similar between the two groups. In HIV positive patients baseline IP-10 concentrations were lower in those who achieved a SVR (84 vs 107 $p=0.02$)

and also differed according to treatment response (SVR, 84 vs RR, 124 vs NR, 107 $p=0.03$).

Conclusion In our cohort IP-10 acted as a robust predictor of SVR among HIV/HCV co-infected and HCV mono-infected patients. IP-10 could serve as a pre-treatment biomarker to help identify patients who will achieve a SVR.

P61 BONE MINERAL DENSITY LOSS IN TENOFOVIR TREATED CHRONIC HEPATITIS B VIRUS (HBV) PATIENTS IS A CONSEQUENCE OF VITAMIN D DEFICIENCY AND NOT TENOFOVIR THERAPY

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Introduction Tenofovir Disoproxil Fumarate (TDF) is now established as a very potent oral antiviral (OAV) agent in the treatment of chronic hepatitis B (CHB). However, as treatment with this OAV is often indefinite and potentially lifelong, concerns remain about its long-term safety. Bone Mineral Density (BMD) loss has been described in TDF treated HIV patients, but limited data exist for HBV treated patients. Furthermore, BMD loss has also been described in chronic liver disease in addition to being reported with certain patient characteristics.

Aim The aim of this study was to determine the impact of TDF on BMD in an ethnically diverse HBV infected population undergoing long-term treatment with this agent.

Method CHB patients treated with TDF for a minimum of 12 months were recruited to this single centre study. Patients were prospectively offered a dual x-ray absorptiometry (DEXA) scan. Serum bone profile and Vitamin D levels were requested simultaneously. BMD loss was defined by WHO criteria; T-score < -2.5 (osteoporosis) and between -1 and -2.5 (osteopenia). 107 consecutive TDF treated patients were included (78 males), median age 45 (range 26–64). A control group, 27 CHB patients (19 males), median age 32 (range 20–61), with no TDF exposure were also studied. Data on gender, ethnicity, BMI, fibrosis stage, co-morbidities and drug history were recorded in all subjects. Analysis was performed with SPSS V.19.

Results BMD loss was present in 44% of the treatment group (osteopenia 81%, osteoporosis 19%) and in 44% of the control group (osteopenia 83%, osteoporosis 17%) ($p=0.21$). In the ethnically diverse population studied, there was more marked BMD loss in the non-white population (47%, treated group; 45%, controls) compared with the white population (30%, treated group; 40%, controls). By univariate analysis age, gender, ethnicity, fibrosis stage, BMI, co-morbidities and low Vitamin D level were all significant for reduced BMD ($p \leq 0.05$, all variables). On multivariate analysis gender, ethnicity, BMI, fibrosis, co-morbidities and Vitamin D all met statistical significance for a reduction in BMD, but Vitamin D deficiency only was significant for the presence of osteoporosis ($p=0.0001$).

Conclusion Our results demonstrate the prevalence of reduced BMD in CHB patients of diverse ethnicity and identify Vitamin D deficiency and not TDF as the likely cause. This cross-sectional study does not exclude the potential for BMD loss with TDF and further longitudinal studies are required to determine its effect on BMD over time. Vitamin D deficiency should be appropriately treated to avoid any potential for BMD loss associated with TDF when considering treatment with this OAV agent.