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.

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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/ m^2 /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.

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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 $<1 \log_{10}$ decline in viral load at week 4. Null response (NR) to a current or prior course of PR is defined as a $<2 \log_{10}$ 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 $-1 \log_{10}$ 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.