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IL28B POLYMORPHISM IS SIGNIFICANTLY CORRELATED WITH IFN ANTI-VIRAL EFFECTIVENESS ALREADY ON FIRST DAY OF PEGYLATED INTERFERON-A AND RIBAVIRIN THERAPY OF CHRONIC HCV INFECTION

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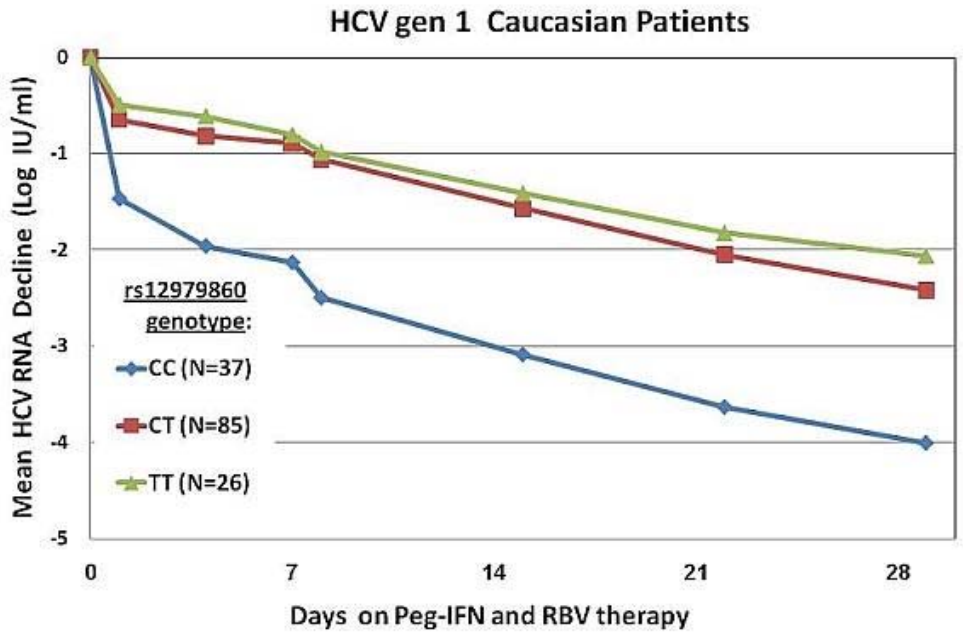
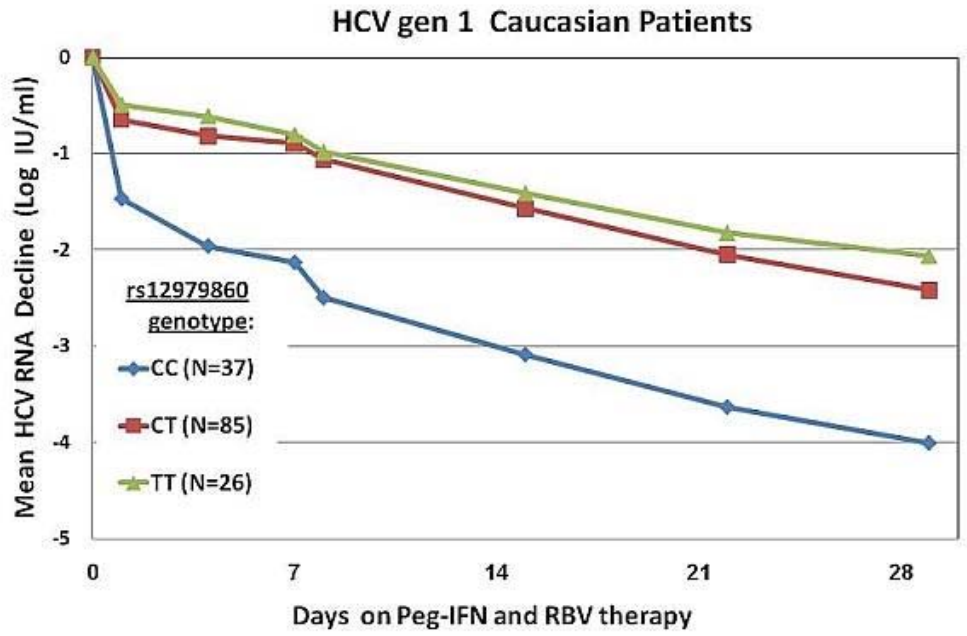
Background & Aims: Recently, single nucleotide polymorphisms (SNPs) in IL28B were shown to correlate with response to pegylated interferon-a (IFN) and ribavirin therapy of chronic HCV infection. However, the cause for the SNPs effect on therapy response and its application for direct anti-viral (DAV) treatment are not clear. Here, we analyze early HCV kinetics as function of IL28B SNPs to determine its specific effect on viral dynamics.
Methods: IL28B SNPs rs8099917, rs12979860 and rs12980275 were genotyped in 252 chronically HCV infected Caucasian naïve patients (67% HCV genotype 1, 28% genotype 2-3) receiving peginterferon-alfa-2a (180 µg/qw) plus ribavirin (1000-1200 mg/qd) in the DITTO study. HCV-RNA was measured (LD=50 IU/ml) frequently during first 28 days.
Results: RVR was achieved in 33% of genotype 1 patients with genotype CC at rs12979860 versus 12-16% for genotypes TT and CT (P< 0.03). Significant (P< 0.001) difference in viral decline was observed already at day 1 (see Figure). First phase decline was significantly (P< 0.001) larger in patients with genotype CC (2.0 log) than for TT and CT genotypes (0.6 and 0.8), indicating IFN anti-viral effectiveness in blocking virion production of 99% versus 75-84%. There was no significant association between second phase slope and rs12979860 genotype in patients with a first phase decline larger than 1 log.



[HCV kinetics as function of IL28b SNP]

The same trend (not shown) was observed for HCV genotype 2-3 patients with different SNP genotype distribution that may indicate differential selection pressure as function of HCV genotype.
Similar results were observed for SNPs rs8099917 and rs12980275, with a strong linkage disequilibrium among the 3 loci allowing to define the composite haplotype best associated with IFN effectiveness.
Conclusions: IFN effectiveness in blocking virion production/release is strongly affected by IL28B SNPs, but not other viral dynamic properties such as infected cell loss rate. Thus, IFN based therapy, as standard-of-care or in combination with DAV, should consider IL28B SNPs for prediction and personalized treatment, while response to pure DAV treatment may be less affected by IL28B SNPs. Additional analyses are undergoing to pinpoint the SNP effect on IFN anti-viral effectiveness.



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