Genetic Factors and Hepatitis C Virus Infection

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It is now possible to comprehensively screen the human genome for genetic variation that influences the outcomes of human disease and pharmacotherapy. The most popular approach remains the genome-wide association study (GWAS), in which many hundreds of thousands of genetic markers, representing common variation across the genome, are tested for association with disease. Two success stories of the GWAS era are reviewed here: the discoveries of the association between interleukin-28B (IL28B) polymorphism and peginterferon-α (pegIFN) and ribavirin (RBV) treatment response for genotype 1 HCV, as well as spontaneous clearance of acute HCV infection, and the association between inosine triphosphatase (ITPA) variation and RBV-induced hemolytic anemia.

The discovery that *IL28B* variation is associated with the response to treatment with peginterferon alfa (pegIFN) and ribavirin (RBV) for genotype 1 hepatitis C virus (HCV) was made by 4 independent groups in late 2009 and early 2010.[1–4] All identified single nucleotide polymorphisms (SNPs) that tag a haplotype block on chromosome 19 spanning *IL28B*, coding for IFN-λ3, and which strongly predict the outcomes for treatment of chronic genotype 1 HCV infection. Individuals who carry the good response variant have an approximately 2-fold higher rate of sustained virological response (SVR) (Table 1). The top discovery SNPs identified in the GWAS included rs12979860[1] and rs8099917[1–4] (note that rs12979860 was only included on the genotyping chip used for the Ge study; rs8099917 was included on the genotyping chips used in all 4 studies). A more comprehensive discussion of GWAS methodology is detailed in Manolio et al,[5] Pearson et al,[6] and Hardy et al.[7] In most populations, these 2 SNPs are in strong linkage disequilibrium and are similarly informative, the exception being individuals of African American ancestry, where rs12979860 is more closely associated with treatment outcome. The frequency of the good response allele differs according to ethnic background; it is more common in individuals of Asian > Caucasian > Hispanic > African ancestry.[1,8] *IL28B* allele frequency explains much of the difference in treatment response rates that have been observed between different populations. The good response variant was also noted to be less common among individuals chronically infected with HCV than healthy controls,[1] consistent with genetic selection. *IL28B* variation was subsequently found to be associated with spontaneous clearance of HCV infection as well.[4,8–10] The effect size is similar, with patients carrying the good response variant being 2-fold more likely to naturally clear acute infection.

IL28B polymorphism is strongly associated with the viral kinetics of IFN response, where the major influence of the good response variant is to enhance phase 1 decline,[11] increasing the rates of critical on-treatment milestones and decreasing relapse (Table 1).[12] *IL28B* genotype is the strongest pretreatment predictor of IFN responsiveness.[12] Once treatment has been started, on-treatment viral decline remains the strongest predictor of viral clearance. Patients carrying the good response *IL28B* variant are more likely to achieve week-4 rapid virological response and week-12 complete early virological response, but once these milestones have been achieved, SVR rates are high regardless of IL28B genotypes (Table 1). *IL28B* genotyping and on-treatment viral kinetics can therefore be considered complementary, one being informative pretreatment, the other requiring a trial of treatment.

The association between *IL28B* genotype and pegIFN and RBV treatment response has been considered in a number of different clinical scenarios. *IL28B* genotype is relevant to the outcomes of pegIFN and RBV treatment for genotype 1 HCV patients co-infected with human immunodeficiency virus, with similar effect size to that seen in HCV monoinfection.[13] It is also relevant to the treatment of genotype 1 HCV in patients after orthotopic liver transplantation.[14,15] Both donor and recipient *IL28B* genotypes have an additive influence on IFN treatment

Abbreviations used in this paper: DAA, direct-acting antiviral agent; HCV, hepatitis C virus; ISG, interferon-stimulated genes; ITPase, inosine triphosphatase; pegIFN, peginterferon alfa; RBV, ribavirin; SNP, single nucleotide polymorphisms; SVR, sustained virological response.

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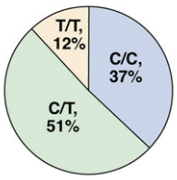
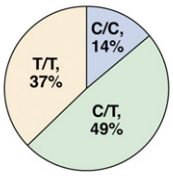
Table 1. Response Rates According to IL28B Genotype (rs12979860) in Treatment-Naïve North American Genotype 1 HCV Patients Receiving 48 Weeks of pegIFN Alfa Plus RBV (Intent-to-Treat Analysis, IDEAL Study Pharmacogenomics Cohort[12])

Peginterferon-α plus ribavirin therapy		rs12979860 C/C	rs12979860 C/T	rs12979860 T/T
Caucasians (n=1171) 	RVR	28%	5%	5%
	cEVR	87%	38%	28%
	Relapse	14%	31%	37%
	SVR	69%	33%	27%
	SVR: if RVR if cEVR	85% 81%	76% 75%	100% 77%
African Americans (n=300) 	RVR	15%	2%	3%
	cEVR	50%	20%	24%
	Relapse	23%	34%	38%
	SVR	48%	15%	13%
	SVR: if RVR if cEVR	100% 84%	100% 58%	100% 58%

NOTE. Ethnicity was defined by self-report. In most populations rs12979860 and rs8099917 are similarly informative due to strong linkage disequilibrium, the exception being individuals of African-American ancestry, where rs12979860 is more closely associated with treatment outcomes.

cEVR, complete early virological response rate, undetectable HCV RNA at week 12; RVR, rapid virological response rate, undetectable HCV RNA at week 4.

outcomes. The association between *IL28B* genotype and treatment response for non–genotype 1 HCVs has been investigated. IL28B genotype is associated with similar predictive utility for SVR in genotype 4 HCV.[16–18] Data evaluating treatment outcomes for genotype 2/3 HCV have been mixed.[4,19] An association with early virological kinetics and rapid virological response, but not necessarily SVR, has been demonstrated. Genotype 2/3 HCV are more sensitive to the antiviral effects of pegIFN and RBV, with 24 weeks of treatment curing >70% of individuals. A relative increase in the rate of viral clearance of a degree similar to that of genotype 1 HCV will not increase the absolute rate of SVR greatly, and most studies to date have not been powered to detect small differences. Therefore, a biological effect might exist, but from a practical perspective, *IL28B* genotype is clearly less relevant to clinical management of most patients chronically infected with genotype 2/3 HCV. It might be important for patients with other poor prognostic factors, such as cirrhosis or slow on-treatment response (non–rapid virological response patients).[10] There are few data yet concerning the treatment of other HCV genotypes.[20] In addition to HCV clearance, *IL28B* polymorphism has also been shown to be associated with HCV viral load set point, HCV lipid disturbance, and hepatic steatosis, as well as histological necroinflammatory activity.

The mechanism by which *IL28B* variation influences viral decline and treatment outcomes remains unclear. Neither rs12979860 nor rs8099917 are likely to be causal, but are instead tag SNPs for a functional variant that is yet to be identified. A number of candidate functional variants have been identified within the haplotype associated with treatment response. Most of these are close to but outside the coding region of the gene, including variants in promoter regions. A single coding variant has been identified, a nonsynonymous SNP in exon 2 (rs8103142, K70R). Linkage disequilibrium in the region is so strong that it has not been possible to differentiate these by association testing. Functional studies of IL28B gene expression and/or IFN-λ3 function will be necessary to identify a single causal variant.[1,21] Early data evaluating *IL28B* gene expression in peripheral blood mononuclear cells have been conflicting; no association between *IL28B* genotype and whole liver *IL28B* gene expression has been observed.[1–3,22,23] The immunological consequences of *IL28B* genotype remain poorly defined. The protein product of *IL28B* is IFN-λ3, a member of the type 3 IFN family. Type 3 IFNs have a unique cellular receptor, with restricted expression relative to the ubiquitous type 1 IFN receptor.[24] They share common downstream signaling pathways to induce expression of interferon-stimulated genes (ISGs) and inhibit HCV replication.[24] Although no direct link between *IL28B* polymorphism, IFN-λ3 signaling, and liver ISG expression has been established in chronic hepatitis C patients, *IL28B* genotype has been associated with differential patterns of intrahepatic ISG

Table 2. Response Rates According to IL28B Genotype in Treatment-Naïve Genotype 1 HCV Patients Receiving Boceprevir/Telaprevir-Based Triple Therapy[28,30]

DAA-based therapy		rs12979860 C/C	rs12979860 C/T	rs12979860 T/T
Boceprevir therapy[a]	Lead-in phase: ≥1 $\log_{10}$ reduction in HCV RNA[c]	97%	75%	56%
	Wk 8 HCV RNA undetectable[d]	89%	52%	
	SVR	80%–82%	65%–71%	55%–59%
Telaprevir therapy[b]	eRVR[d]	78%	57%	45%
	SVR	90%	71%	73%

NOTE. Data presented are for patients receiving boceprevir therapy in the SPRINT-2 study unless otherwise indicated.[30]

[a]Data presented are for patients receiving 12 weeks of telaprevir therapy combined with 24 or 48 weeks of pegIFN alfa + RBV in the ADVANCE trial.[28]

[b]Data represent a combined analysis of patients receiving boceprevir in the SPRINT-2 and RESPOND-2 studies.[30]

[c]Decision point for short vs long duration therapy using response-guided therapy.