

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## New Genetic Findings to Predict Treatment Success in Hepatitis C

John G. McHutchison, MD and  
Alexander J. Thompson, MD, PhD  
Duke Clinical Research Institute and  
Division of Gastroenterology  
Duke University  
Durham, NC

### **G&H** Can you describe the design and original endpoint for the IDEAL study?

**JM/AT** The IDEAL study was a three-armed study conducted in the United States looking at treatment-naïve patients with genotype 1 hepatitis C virus (HCV) infection. There were approximately 1,000 patients in each arm, for a total of about 3,000 patients in the trial, which compared pegylated interferon (PegIFN)-alfa-2b at doses of 1 mcg/kg and 1.5 mcg/kg, both weekly, plus weight-based ribavirin (RBV), daily. In the third arm of the trial, patients received PegIFN-alfa-2a at standard dosing, also with RBV. IDEAL was conducted as a post-approval commitment to the US Food and Drug Administration. The endpoint of the trial was sustained virologic response (SVR) to therapy, defined by negative HCV RNA, 24 weeks after the end of therapy. Final results showed similar efficacy across all three arms.

### **G&H** How was the IDEAL cohort utilized to study genomic associations with treatment success?

**JM/AT** When we began recruitment for the study, we realized that it presented an opportunity to examine genetic influences on treatment response. At the inception of the study, we provided a separate consent form to participants, which asked them to allow us to collect a DNA sample that would subsequently be utilized to

perform our genome-wide comparison looking for associations with treatment response. A little over half of the IDEAL patients agreed to participate, and we ended up with approximately 1,600 patients in our study.

### **G&H** Was the comparison targeted to specific genes, or did you compare all patients across the entire DNA sample?

**JM/AT** We compared all patients using a genome-wide analysis scan or chip. The Illumina 610 chip sequences over 600,000 single nucleotide polymorphisms (SNPs); these SNPs have been specifically chosen to cover over 90% of the common variations in the human genome. This is possible because of linkage disequilibrium, where two SNPs that are located near each other on a chromosome are inherited together, and testing one allows inference of the sequence at the other. In practical terms, this means that we have over 90% coverage of the allelic variants/SNPs that are present in more than 5% of the population.

### **G&H** How did you analyze the data, and what did you find?

**JM/AT** Each SNP was tested individually for association with SVR in a logistic regression model. Because there

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were almost 600,000 SNPs included in the final analysis, the likelihood of a false-positive association in our analysis was extremely high. Bonferroni correction of *P* values was therefore necessary, meaning that the threshold for a statistically significant association was *P* less than  $10^{-8}$ .

Ultimately, we found 7 polymorphisms that were associated with SVR beyond the  $10^{-8}$  threshold. All of the associated SNPs were on a single haplotype block in the region of the *IL28B* gene on chromosome 19. The most strongly associated SNP is located just upstream of the *IL28B* gene, which is also known as IFN lambda 3. The *P* value for this association was  $10^{-28}$ , far exceeding genome-wide significance. We observed that in white patients with the favorable variant of this polymorphism, and who were adherent to therapy, the likelihood of achieving SVR was over 80%, over double that achieved by patients with either of two other variants at this position (Table 1).

The other very interesting finding was that the population frequency of the good-response variant was very different between whites and African Americans. The favorable response variant was much more common in whites (39% vs 16% in African Americans, Table 1). This discrepancy was estimated to explain about half of the difference in response rates to HCV therapy that is observed between the two groups.

#### G&H Were you able to pinpoint any specific polymorphisms with a negative predictive value?

**JM/AT** This is really the other side of the same coin. At each polymorphism, there are three different possible genotypes. In the case of the *IL28B* polymorphism, there is the good-response variant (C/C) and the other two variants (C/T, T/T). The good-response variant is associated with a strong positive predictive value, which could be similarly calculated as a strong negative predictive value for the other variants at the same position.

#### G&H What other research is necessary to fully explain the difference in outcomes among different ethnic groups?

**JM/AT** As mentioned above, the *IL28B* polymorphism explains more than half of the difference in racial response between whites and African Americans. Furthermore, we also know that Asians have a very high prevalence of the favorable polymorphism and they have a very high response rate to treatment for HCV. Hispanics have an intermediate frequency in the gene between African Americans and whites, and they have an intermediate response rate. Thus, attributes that had previously been assigned to skin color and race can now be explained by this gene instead. However, it is likely that

**Table 1.** Population Frequency of *IL28B* Genotype, and Corresponding SVR Rates in Adherent Genotype 1 HCV Patients Treated with PegIFN and RBV

	<b>IL28B genotype population frequency</b>	<b>SVR rate</b>
<b>Whites (n=871)</b>		
C/C	39%	82%
C/T	49%	42%
T/T	12%	33%
<b>African Americans (n=191)</b>		
C/C	16%	53%
C/T	48%	19%
T/T	36%	17%

Data from Ge et al. *Nature*, 2009.

there are other genetic factors involved, particularly in the African-American population. Otherwise, patients without the gene would have a 0% response rate and those with it would have 100% SVR. This will require further study.

#### G&H What are the practical applications of these findings in the clinical setting? Will they lead to new therapeutic targets?

**JM/AT** For clinical practice, we believe that knowledge of the *IL28B* genotype will be useful for making treatment decisions in patients with genotype 1 HCV. We now have two factors that are most important in predicting treatment response. The most important pretreatment factor is the presence of the good response C/C *IL28B* genotype. The most important on-treatment factor is the achievement of rapid viral response at 4 weeks. Patients want to be tested for this polymorphism before undergoing therapy, and we are already fielding inquiries. However, it is not yet available commercially. We hope that the diagnostic test will be available in the near future, so that patients can be tested easily and the results discussed with their physician. Essentially, physicians can now tell their patients that if they have the polymorphism, they have an 80% chance of achieving SVR. If they do not have it, they have only a 30–40% chance of SVR.

In terms of potential therapeutic targets, we do not yet know what this polymorphism does, functionally or biologically. We do not yet know the effect on *IL28B*

gene expression or signaling, nor do we know why it affects the efficacy of PegIFN plus RBV therapy for genotype 1 HCV. These are important questions, and we look forward to an exciting new era in HCV basic and translational research.

It should be noted that IL29, another member of the IFN-lambda family, which signals via the same receptor as IL28B, is already in a clinical development program for genotype 1 HCV. Early results have shown an antiviral effect. Whether the identification of this polymorphism is relevant to IL29 therapy is not yet known.

### Suggested Reading

Rauch A, Kutalik Z, Descombes P, Cai T, di Iulio J, et al.; Swiss Hepatitis C and HIV Cohort Studies. Genetic Variation in IL28B Is Associated with Chronic Hepatitis C and Treatment Failure—A Genome-Wide Association Study. *Gastroenterology*. 2010 Jan 7. [Epub ahead of print]

Pos Z, Sella S, Spivey TL, Wang JK, Liu H, et al. Genomic scale analysis of racial impact on response to IFN-alpha. *Proc Natl Acad Sci U S A*. 2010;107:803-808.

Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009;461:399-401.

Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet*. 2009;41:1100-1104.

Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet*. 2009;41:1105-1109.

McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, et al.; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;361:580-593.

Su X, Yee LJ, Im K, Rhodes SL, Tang Y, et al.; Virahep-C Study Group. Association of single nucleotide polymorphisms in interferon signaling pathway genes and interferon-stimulated genes with the response to interferon therapy for chronic hepatitis C. *J Hepatol*. 2008;49:184-191.

Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009;461:789-801.