Utility of IL-28B Polymorphisms in the Era of Direct-Acting Antiviral Therapy

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G&H Why is interleukin-28B genotype information useful when treating patients with hepatitis C virus infection?

SCG Several viral and host factors help to predict the likelihood of virologic response to pegylated interferon (peginterferon) and ribavirin in patients with hepatitis C virus (HCV) infection. For example, factors that make a patient more likely to respond to such treatment include lower baseline viral levels, less liver fibrosis, lower body weight, and infection with HCV genotypes other than 1 and 4. Racial background also influences treatment response, with Asians responding far better to treatment than whites or individuals of African descent.

In addition, patients with HCV genotype 1 infection who are homozygous for the CC allele of the single nucleotide polymorphism (SNP) rs12979860 have much higher sustained virologic response (SVR) rates following a course of peginterferon and ribavirin therapy than patients with CT or TT alleles; such differences partly explain the lower response rates among black patients. The presence of the interleukin (IL)-28B CC genotype is also strongly associated with rapid virologic response, which among white patients was shown to be the strongest predictor of SVR.

G&H Have any studies examined the predictive value of IL-28B genotype for patients receiving telaprevir- or boceprevir-based treatment?

SCG Post-hoc analyses of studies involving telaprevir (Incivek, Vertex) or boceprevir (VICTRELIS, Merck) have examined the predictive value of IL-28B genotype for patients receiving triple therapy. However, such analyses were limited to subjects who consented for these retrospective analyses. Also, because the discovery of the IL-28B gene and its significance occurred after the start of these studies, patients were stratified irrespective of IL-28B status.

IL-28B testing was performed in nearly two thirds of the patients in the boceprevir trials SPRINT-2 and RESPOND-2, which involved treatment-naïve patients and prior treatment failures, respectively. In both trials, patients with the CC genotype were more likely to achieve SVR than non-CC patients. In both SPRINT-2 and RESPOND-2, the presence of the IL-28B CC polymorphism (vs a non-CC polymorphism) was a strong predictor of viral negativity at Week 8 (89% vs 52% in SPRINT-2; 82% vs 51% in RESPOND-2). In the trial of treatment-naïve patients, IL-28B CC genotype (vs a non-CC genotype) remained predictive of SVR in a multiple stepwise logistic regression model.

When considering these data, clinicians should keep in mind that patients in the boceprevir trials received 4 weeks of lead-in therapy with peginterferon and ribavi-
prior relapers, partial responders, and null responders, however, the difference between CC and non-CC genotype was smaller. peginterferon and ribavirin in addition to telaprevir for both boceprevir- and telaprevir-based regimens. In all the studies evaluating triple therapy regimens, SVR rates remained high among CC-genotype, treatment-naïve individuals in the peginterferon and ribavirin control group. Given that patients with the CC genotype do well with peginterferon and ribavirin alone, some clinicians have questioned the relevance or added benefit of triple therapy in this subpopulation. Although CC-genotype, treatment-naïve patients actually do well when treated with 48 weeks of peginterferon and ribavirin, the majority of patients in this subgroup would also be eligible for a shortened duration of triple therapy; this advantage has been demonstrated for both boceprevir- and telaprevir-based regimens. In contrast, peginterferon and ribavirin therapy can only be shortened in those few patients who become HCV RNA–negative at Week 4. Thus, the main advantage of triple therapy in the IL-28B CC population is its ability to shorten treatment duration.

**G&H** Is triple therapy necessary in patients who have a favorable IL-28B genotype?

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**G&H** Can IL-28B genotype information help to guide decisions about boceprevir- or telaprevir-based triple therapy?

**SCG** IL-28B testing provides some helpful information regarding the likelihood of SVR with telaprevir- or boceprevir-based triple therapy regimens. Among treatment-naïve individuals, patients with the CC genotype have a high likelihood of responding to triple therapy and are more likely to be eligible for a shortened treatment duration by virtue of the fact that they are more likely to achieve a rapid virologic response.

**G&H** What are the limitations of IL-28B genotype testing?

**SCG** Similar to all predictive parameters, IL-28B genotype information is valuable at the population level, but other factors interact with genotype to determine treatment response in each individual. Thus, a favorable or unfavorable genotype may prove incorrect in predicting response in a given patient. For example, black patients as a group are less likely to respond to peginterferon and ribavirin therapy, but some black individuals still do very well with this therapy. Clinicians therefore need to remember that the positive and negative predictive values calculated in clinical trials are nothing more than an expression of statistical odds ratios. On-treatment response is more predictive of ultimate viral cure for an individual patient.

Another limitation of IL-28B genotyping is that this testing remains expensive. In an era of exorbitant medical costs, clinicians should consider the rationale for using this test and decide whether it will alter the patient’s management, rather than just ordering this test for every patient.

**G&H** What further research is needed regarding the utility of IL-28B testing?

**SCG** A 2010 meeting of experts from academia, government, and industry identified several future research directions related to IL-28B testing. Specifically, this panel recommended further study of the biology of IL-28B (eg, how λ interferons affect HCV suppression and how IL-28B correlates with clinical manifestations of disease), additional monitoring of treatment efficacy in various subpopulations (including black individuals and post-transplant patients), and more research regarding the cost-effectiveness of IL-28B genotyping.

**G&H** Which other genetic polymorphisms yield predictive information in telaprevir- or boceprevir-treated patients?

**SCG** A 2009 report from Duke University described several highly correlated SNPs in the vicinity of 3 interferon λ genes, each of which was highly predictive of response to peginterferon and ribavirin therapy in HCV genotype 1–infected patients. The 3 genes (IL-29, IL-28A, and IL-28B) are also associated with the natural clearance of HCV, even HCV acquired by vertical transmission.
Additionally, 2 polymorphisms in the *ITPA* gene predict which patients are likely to develop ribavirin-induced hemolytic anemia during antiviral therapy. Testing for these polymorphisms could help tailor therapy based on a patient’s propensity for tolerating the various components of antiviral therapy.

**G&H** Do the higher SVR rates attainable with telaprevir- and boceprevir-based treatment regimens negate the benefit of IL-28B genotype information?

**SCG** Evidence is emerging that more potent HCV treatment regimens may overwhelm the *IL-28B* C allele advantage. For example, a presentation at the 2011 Annual Congress of the European Association for the Study of the Liver assessed patients who were enrolled in the TMC435 study and found that, while *IL-28B* genotype was useful for predicting response in patients receiving peginterferon and ribavirin, this parameter had limited predictive value in patients treated with TMC435 plus peginterferon and ribavirin. This finding suggests that the addition of more potent oral protease inhibitors may overcome the negative consequences of unfavorable host genotypes.

**Suggested Reading**


