Published in final edited form as:
Clin Gastroenterol Hepatol. 2011 April ; 9(4): 293–294. doi:10.1016/j.cgh.2010.12.014.

IL28B-Genotype Testing Now and in the Era of Direct-Acting Antiviral Agents

Timothy R. Morgan, MD and
Chief, Hepatology, VA Long Beach Healthcare System And Professor of Medicine, University of California-Irvine, timothy.morgan@va.gov

Thomas R. O'Brien, MD, MPH
Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, obrient@exchange.nih.gov

Peginterferon alfa and ribavirin treatment for 48 weeks leads to a sustained virological response (SVR) in 40 – 50% of subjects infected with HCV genotypes 1 or 4 (G1/4) while treatment for 24 weeks produces SVR in 70 – 80% of patients infected with HCV genotypes 2 or 3. The variability in response to treatment, especially between patients of different racial groups, suggested that human genetic variability might explain differences in treatment response and led to investigations of the role of host genetics in achieving an SVR.

Genome wide association studies (GWAS), which examine the association between >500,000 single nucleotide polymorphisms (SNPs) and a disease of interest, have been exceptionally successful in finding SNPs associated with response to hepatitis C treatment. In 2009, three groups reported that SNPs located near the gene for interleukin-28B (*IL28B*) were strongly associated with the likelihood of achieving an SVR with peginterferon + ribavirin treatment[1–3]. *IL28B* encodes a protein that is also known as interferon lambda-3 (IFN-λ3), a type III interferon. The receptors for interferon alpha, a type I interferon, differ from those for IFN-λ3, but both IFN-λ and IFN-α activate the same intracellular pathway (Jak/STAT), which results in expression of many interferon stimulated genes[4–6].

SNPs rs12979860 and rs8099917, respectively located 3 and 8 kb upstream of *IL28B*, were the variants most strongly associated with treatment response in these studies. Among treatment naïve G1-infected subjects of European ancestry who were enrolled in the IDEAL study, approximately 69% of those who carried two C alleles (C/C) at rs12979860 achieved an SVR compared to 33% of those with the C/T genotype and 27% with genotype T/T[7]. Consistent findings were reported for rs8099917 among Japanese, Australian and European populations2–3. These studies demonstrated that carriage of two *IL28B* favorable alleles strongly, but not fully, predicted SVR, while carriage of one or two unfavorable alleles did

Correspondence to: Timothy R. Morgan.

Conflict of Interest:
Timothy R. Morgan has received research support from the following: Genentech, Vertex, Merck, and WAKO Diagnostics. Thomas R. O'Brien has no Conflict of Interest to disclose.

not completely predict failure to respond to treatment. It appears that rs12979860 is more predictive of SVR than rs8099917, especially among people of African ancestry in whom rs8099917 is less polymorphic than rs12979860[1].

In the current issue of Clinical Gastroenterology and Hepatology, Stattermayer and colleagues performed *IL28B* genotype testing for rs12979860 and rs8099917 in 682 Austrian subjects (G1=372; G2/3=208; G4=102) who completed treatment with peginterferon and ribavirin and agreed to return for genetic testing[8]. They found that subjects infected with G1/4 who carried two C alleles at rs12979860 (i.e., the most favorable genotype) had a greater decline in HCV RNA 24 hours after the first injection of interferon than did G1/4-infected subjects who carried a T allele (either C/T or T/T). Similarly, subjects infected with G1/4 who carried rs12979860 C/C were more likely to achieve a rapid virological response (RVR; G1: 38% vs. 12%) and SVR (G1: 79% vs. 43%) as compared with carriers of the T allele. Among subjects infected with G2/3, rs12979860 C/C carriers had a higher likelihood of RVR (75% vs. 53%), but the difference for SVR (81% vs. 72%) did not reach statistical significance. *IL28B* rs12979860 genotype was the strongest pretreatment predictor of SVR, but when the initial response to peginterferon and ribavirin was considered, RVR rather than *IL28B* genotype was the strongest predictor of SVR in this population. The authors concluded that *IL28B* genotype influenced the rate of initial viral decline with peginterferon/ribavirin treatment and that *IL28B* genotype, in conjunction with RVR, might be useful parameters in predicting SVR in G1/4 subjects.

The findings of Stattermayer and co-workers confirm prior reports of *IL28B* genotype testing among subjects treated with peginterferon + ribavirin. Several investigators have reported that subjects with rs12979860 C/C have a greater initial decline in HCV RNA level and a higher likelihood of achieving RVR and SVR[1, 7, 9]. Thompson reported that *IL28B* genotype is the most important pretreatment variable to predict SVR, but *IL28B* genotype loses importance as a predictor of SVR when RVR is included in a multivariate analysis[7]. Stattermayer confirmed that rs12979860 is more informative than rs8099917 as a pretreatment predictor of SVR among those of European ancestry[1]. In total, studies from Stattermayer and others show a strong association of *IL28B* genotype with virological response to peginterferon + ribavirin treatment, including the rate of early viral decline and the likelihood of achieving RVR and SVR.

The human genome project promised to introduce an era of 'personalized medicine,' in which genetic testing would be used to predict the likelihood of clinical outcomes, including response to drugs, in individual patients[10]. In June 2010 the Food and Drug Administration approved a test for rs12979860 genotype, which has been licensed to several clinical laboratories. Gastroenterologists now must decide whether to obtain *IL28B* genotype for their HCV-infected patients and, if so, how to incorporate these results into decisions regarding hepatitis C treatment. *IL28B* genotype joins a considerable list of pretreatment factors that have been shown to predict the probability of SVR, including HCV genotype, HCV RNA level, severity of liver fibrosis, and racial ancestry. Information on each of these factors can help inform the physician and patient of the likelihood of achieving an SVR, however, none alone is sufficient to guarantee or preclude the possibility of achieving an SVR. Although *IL28B* genotype alone is insufficient for deciding whether or not a patient is likely to respond to peginterferon and ribavirin, we believe that mathematical clinical prediction models based on *IL28B* genotype and clinical characteristics may prove useful for predicting SVR. Indeed, among interferon non-responders who were retreated with peginterferon + ribavirin in the HALT-C Trial, we have presented 'proof of concept' that a model that includes *IL28B* plus some commonly measured clinical variables (HCV viral load, liver fibrosis score and AST/ALT ratio) has good discrimination and predictive ability for the probability of SVR [11]. If validated, such a model could be used to calculate

individually tailored probabilities of achieving an SVR for patients. Clinical prediction models may also be useful for on-treatment predictions of SVR.

The availability of *IL28B* genotype testing to help predict SVR coincides with another major advance in the treatment of chronic hepatitis C, the introduction of direct-acting antiviral agents (DAAs) that specifically target enzymes critical to HCV replication. At this writing, it appears likely that two HCV-specific protease inhibitors, boceprevir and telaprevir, will be approved by the FDA in 2011. Data from clinical trials suggest that adding a protease inhibitor to the peginterferon + ribavirin regimen increases the overall SVR rate among treatment naïve G1-infected patients to 65 – 75%[12–13]. However, adding a viral protease inhibitor to current standard of care is not without additional risks. Patients taking these agents are subject to several potential adverse effects, including anemia and skin rash. Furthermore, patients who fail to achieve SVR on a regimen that includes a protease inhibitor will likely harbor resistant viruses that limit future use of protease inhibitors in that patient. Initial studies suggest that *IL28B* genotype may be predictive of response to treatment with protease inhibitors, too. Among Japanese patients who received telaprevir + peginterferon + ribavirin, Akuta and colleagues reported an SVR rate of 83% for subjects carrying rs12979860 C/C as compared with 32% among subjects who carried a T allele[14]. If confirmed in other populations, these data suggest that carriers of the less favorable *IL28B* genotypes will be less likely to respond to triple therapy that includes protease inhibitors and raise the possibility that *IL28B* genotype based models may be useful for predicting the likelihood of SVR in response to treatment with peginterferon + ribavirin + protease inhibitors.

Until now, the outcome of treatment for chronic hepatitis C could be broadly classified as either successful (SVR) or futile (non-response). The advent of the DAA era promises to increase the number of patients for whom treatment is successful, but also introduce a third outcome – patients who not only fail treatment, but also harbor resistant viral strains that may compromise future treatment options. Thoughtful incorporation of *IL28B* genotyping into treatment decision-making may serve to increase the number of patients for whom treatment is successful while minimizing those in whom it is deleterious.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government

References

1. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009; 461:399–401. [PubMed: 19684573]
2. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet. 2009; 41:1100–1104. [PubMed: 19749758]
3. Tanaka Y, Nishida N, Sugiyama M, 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. [PubMed: 19749757]
4. O'Brien TR. Interferon-alfa, interferon-lambda and hepatitis C. Nat Genet. 2009; 41:1048–1050. [PubMed: 19749756]
5. Kotenko SV, Gallagher G, Baurin VV, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol. 2003; 4:69–77. [PubMed: 12483210]
6. Sheppard P, Kindsvogel W, Xu W, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol. 2003; 4:63–68. [PubMed: 12469119]

7. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010; 139:120–129. e18. [PubMed: 20399780]

8. Stattermayer A, Stauber R, Hofer H, et al. Impact of the IL28B-genotype on early and sustained virologic response in treatment -naive patients with chronic hepatitis C treated with Peg-interferon-alfa2a and ribavirin. Clin Gastroenterol Hepatol. 2010

9. McCarthy JJ, Li JH, Thompson A, et al. Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. Gastroenterology. 2010; 138:2307–2314. [PubMed: 20176026]

10. Feero WG, Guttmacher AE, Collins FS. Genomic medicine--an updated primer. The New England journal of medicine. 2010; 362:2001–2011. [PubMed: 20505179]

11. O'Brien TR, Everhart JE, Chung RT, et al. An IL28B genotype-based model for personalized prediction of response to pegylated-interferon-alfa and ribavirin in the treatment of chronic hepatitis C. Hepatology. 2010; 52:382A. (abstract). [PubMed: 20583194]

12. Bacon BR, Gordon SC, Lawitz EJ. HCV RESPOND-2 final results: High sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus Pegintron/ribavirin. Hepatology. 2010; 52 abstract 216.

13. Jacobson IM, McHutchison J, Dusheiko GM. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study. Hepatology. 2010; 52 Abstract 211.

14. Akuta N, Suzuki F, Hirakawa M, et al. Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. Hepatology. 2010; 52:421–429. [PubMed: 20648473]