Interleukin 28B Polymorphisms and Hepatitis C—Translating the Association into Clinical Decision Making

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ABSTRACT

Host genetic factors have long been suspected to play a role in predicting outcome and treatment response in hepatitis C virus (HCV) infection. This was confirmed recently by three landmark genome-wide association studies (GWAS) published in 2009, which identified single nucleotide polymorphisms near the interleukin (IL) 28B region that were more common in responders to treatment. There has subsequently been rapidly increasing data regarding the significance of the IL28B polymorphism not only in response to therapy but also in spontaneous clearance of acute HCV infection. This clinical association of Il28B genotype with HCV may lead to personalized HCV therapy, where the clinician may tailor the duration and type of therapy for an individual patient. This review summarizes the available data on the impact of IL28B polymorphisms on HCV infection and discusses the possible approach to translate this association into clinical decision making for the treatment of HCV infection.

INTRODUCTION

Hepatitis C virus (HCV) affects approximately 2.2–3% of the population in the world. Natural history studies indicate that only few of the individuals who develop acute HCV infection will clear the virus spontaneously. Of the remaining 55–85% of the patients who become chronically infected, approximately 5–25% will ultimately develop cirrhosis over 25–30 years and a significant proportion will go on to develop hepatocellular carcinoma (HCC).[1–8]

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Abbreviations: ALT: alanine transaminase; EVR: early virological response; GWAS: Genome-wide Association Studies; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN: interferon; IL28B: interleukin 28B; NVR: null virological response; OR: odds ratio; PEG-IFN: pegylated interferon; RBV: ribavirin; RNA: ribonucleic acid; RVR: rapid virological response; SNP: single nucleotide polymorphism; SVR: sustained virological response
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EVOLUTION OF HEPATITIS C VIRUS THERAPIES

Interferon (IFN) therapy is the backbone in the therapy of HCV, with an aim of eradicating the virus and altering the natural history of the disease. Standard IFN-α2a, IFN-α2b, and consensus IFN treatments given as thrice weekly injections for 12 months were associated with an sustained virological response (SVR) of 5–15%.[9] Treatment approaches to chronic HCV infection have improved substantially in the past decade, and therapeutic strategies of HCV infection have evolved from IFN monotherapy to IFN–ribavirin (RBV) combination regimens, and now, pegylated interferon (PEG-IFN)-α2a or α2b plus RBV. Today, the standard of care for patients with chronic HCV infection is PEG-IFN-α2a (180 μg/wk) plus RBV (1000–1200 mg/day) or PEG-IFN-α2b (1.5 μg/Kg/wk) plus weight-based RBV (800–1400 mg/d) for 24 or 48 weeks, depending on the HCV genotype. PEG-IFN and RBV combination therapy is associated with a SVR of 42–46% in HCV genotype 1 and 75–82% in HCV genotypes 2 and 3 patients.[10,11]

PREDICTORS OF RESPONSE IN HEPATITIS C VIRUS

Although the evolution of therapeutic strategies for chronic HCV infection has been accompanied with a progressive improvement in SVR rates, 20–50% of patients treated with PEG-IFN and RBV will not achieve an SVR.[2] A number of factors have been evaluated to predict response. SVR rates were higher in patients infected with genotype non-1 infection (mostly genotypes 2 and 3) and in those with a viral load of < 600,000 IU/mL.[12] Other pretransplant factors, which have been associated with a favorable response, include the doses of PEG-IFN (1.5 μg/Kg/wk vs 0.5 μg/Kg/wk) and RBV (>10.6 mg/Kg), female gender, age <40 years, non-African-American race, lower body weight (≤75 Kg), absence of insulin resistance, elevated alanine transaminase (ALT) levels (3-fold higher than the upper limit of normal), and absence of bridging fibrosis or cirrhosis on liver biopsy.[2] Viral kinetics, including rapid virological response (RVR) and early virological response (EVR), are also being used to predict outcome and guide duration of therapy.

The patient's ancestry is one of the factors affecting treatment outcome with African-American patients with chronic HCV having about 50% reduction in SVR rates with PEG-IFN plus RBV compared with non-Hispanic patients of European ancestry.[13,14] Such ethnic and racial differences suggest that host genetic differences influence the response to HCV treatment. Not only is the treatment of HCV associated with inadequate response rates, it is also expensive and has significant adverse effects. This has led to a growing interest in genetic studies to identify those individuals who are more likely to respond to the treatment regimen.

SEARCHING FOR GENETIC FACTORS

The human genome contains over 3.3 billion base pairs and >10 million of these may vary in nucleotide sequence between individuals, some of which may result in altered gene expression, altered processing of the gene product, or altered functional activity.[15] Identifying polymorphisms that result in altered clinical expression may be like finding a needle in a haystack.[16]

In the initial genetic studies, candidate gene approaches have been utilized to identify polymorphisms influencing treatment response in HCV infection. In the candidate gene approach, investigators conducting genetic association studies may target genes for investigation according to the known or postulated biology and previous results. The earlier approach has its limitations. It is biased in the choice of the candidate gene(s) for study, by the researcher's work and knowledge of the disease. Many studies were underpowered, did not have control groups, or were not replicated, and these studies did not result in an insight as to the role of genetic variation.[17–22]

GENOME-WIDE ASSOCIATION STUDIES

Advancement in technology has now made it possible to screen the entire human genome for variations associated with human diseases. With Genome-wide Association Studies (GWAS), researchers can now investigate a broad spectrum of single nucleotide polymorphisms (SNPs) across the entire genome, without any previous hypotheses about potential mechanisms or suspected polymorphisms. GWAS have led to the discovery of SNPs located near the gene for interleukin 28B (IL28B) gene, which encodes IFN-λ3, which is related to chronic HCV treatment response and the clearance of virus after acute infection. The prediction of treatment outcome for HCV with PEG-IFN plus RBV has been revolutionized by this discovery of the association between SNPs near IL28B gene and SVR.

In 2009, 3 independent GWAS published almost concurrently reported SNPs near the IL28B region that was more common in responders. These patients were mainly of genotype 1 and had been treated with PEG-IFN and RBV. Ge et al were the first to conduct GWAS analysis to investigate genetic predictors of treatment response in HCV.[23] They analyzed 1137 patients, which included Caucasians, African-Americans, and Hispanics. They discovered that SNP rs12979860 was associated with response to therapy with PEG-IFN/RBV. Two other SNPs, not present on the genome-wide chip, were shown to be associated with rs12979860 by fine sequencing studies: rs28416813, lying in the promoter region 37 base pairs upstream of the IL28B start codon, and rs8103142, a non-synonymous polymorphism in exon 2 (Lys70Arg). Since the degree of correlation was high, it was not possible to resolve which of these 3 polymorphisms might be solely responsible for the association signal. Tanaka et al[24] evaluated polymorphisms associated with response to PEG-IFN/RBV in 142 Japanese. Suppiah et al studied genetic variants associated with genetic variants associated with PEG-IFN/RBV therapy in 293 Australians.[25] In 2010, Rauch et al reported their results in 465 Caucasians.[26] The results of all these studies are shown in Table 1.

The exact polymorphisms identified by the different workers do not match. While Ge et al identified rs12979860 as the most important SNP,[23] the papers by Tanaka et al, Suppiah et al, and Rauch et al identified different SNPs, of which, the SNP rs8099917 was the most significant contender.[24–26] However, all the SNPs are in proximity to the IL28B region of chromosome 9 and the 2 major distinct polymorphisms rs12979860 and rs8099917 are in linkage disequilibrium, suggesting the primary role of IL28B gene product IFN-λ3 in determining the clearance of HCV.

CLINICAL IMPLICATIONS OF INTERLEUKIN 28B POLYMORPHISMS ASSOCIATIONS

Chronic Hepatitis C: Genotype 1

Three independent original GWAS have identified variants within the IL28B gene region that are strongly associated with response to PEG-IFN + RBV combination therapy in patients' chronic infection with genotype 1 HCV.

In the initial report by Ge et al, the SNP rs12979860 was strongly related to SVR in genotype 1 patients.[23] The primary analysis for treatment outcome compared SVR with true biological non-response in 1137 patients, in 3 independent ethnic groups—Caucasians, African-Americans, and Hispanics. The favorable C/C genotype was associated with greater rates of SVR than the unfavorable T/T genotype. The SVR rates were ~80% for C/C genotype, ~40% for T/C genotype, and ~30% for T/T genotype. The C/C genotype was more influential than race in predicting SVR. While African-Americans are usually poor responders to IFN therapy, the C/C genotype was associated with SVR in them, although at a lower SVR rate as compared with Caucasians (53% vs ~80%). The differences in SVR across various ethnic groups were related to the C allele frequency. The C allele frequency was ~90% in East-Asian patients,

Table 1 Genome-wide Association Studies of Interleukin 28B gene polymorphisms in treatment of hepatitis C virus.

Characteristics	Ge et al[23]	Tanaka et al[24]	Suppiah et al[25]	Rauch et al[26]
Number	1137	142	293	465
HCV genotype	1	1	1/2/3/4	1/2/3
Region	North America	Japan	Australia, Europe	Switzerland
Race	Caucasians, African-Americans, Hispanics	Japanese	Caucasian	Caucasian, African-Americans
Outcome	SVR vs no SVR	NVR* vs EVR NVR vs SVR	SVR vs no SVR	SVR vs no SVR
Major SNP identified				
rs12979860	+			
rs8099917		+	+	+
rs12980275		+		
rs7248668				
rs11881222		+		
rs8105790		+		+

HCV: hepatitis C virus, SVR: sustained virological response, NVR: null virological response, EVR: early virological response, SNP: single nucleotide polymorphism.
*Null virological response (<2log$_{10}$IU/mL reduction in serum HCV RNA at week 12 of therapy).

~55% in European-American patients, and ~25% in African-American patients.

Suppiah et al found rs8099917 to be strongly related to the SVR.[25] Homozygotes for the minor allele (G/G) had an SVR rate of 31%, while those with genotype T/T had an SVR rate of 56%.

Tanaka et al in their study of genotype 1 in Japanese patients found that rs8099917 and rs12980275 were associated with non-response to treatment.[24] The association analysis used, null virological response (NVR) rather than SVR. NVR was defined as a <2log$_{10}$IU/mL reduction in serum HCV ribonucleic acid (RNA) by week 12 of therapy and detectable HCV RNA at week 24. They found that the G allele was associated with lower SVR (0% in genotype G/G vs 78% in genotype T/T).

In the study by Rauch et al, rs8099917 was associated with response to therapy in genotype 1, unlike that in the small number of genotype 2 or 3 in their study.[26]

The impact of rs12979860 genotype on the possibility of achieving SVR has been analyzed in a meta-analysis of patients infected with genotype 1. The prevalence of genotypes is 35% for genotype C/C, 50% for genotype C/T, and 15% for genotype T/T. The SVR rates for the various genotypes are 80% for C/C, 50% for C/T, and 2% for T/T. The overall response rates were 56% (C/C 28%, C/T 25%, and T/T 3%).[27]

Overall, patients with favorable SNP had an SVR rate of 60%, while those with an unfavorable SNP had an SVR rate of 30%.[28–31] Meta-analysis of SNP of the IL28B and SVR of patients with chronic HCV to PEG-IFN/RBV therapy has shown that the SVR was higher in patients with C/C allele of rs12979860 and the T/T allele of rs8099917 compared with C/T or T/T alleles of rs12979860 and the T/G or G/G allele of rs8099917, respectively.[32]

Stattermayer et al have shown that an EVR to PEG-IFN plus RBV is more likely in carriers of rs12979860 C/C and rs8099917 T/T, which might underlie their high rates of SVR.[33]

Chronic Hepatitis C: Non-genotype 1

Most of the initial studies of HCV and IL28B gene polymorphisms were done on genotype 1 HCV infection. However, further data concerning the relevance of IL28B polymorphism in non-genotype 1 HCV infection is now emerging. Unlike genotype 1, with regard to genotype 2/3, the IL28B polymorphisms have some differences:

(a) The studies of IL28B polymorphism in genotype 2/3 have shown varying results: Mangia et al, showed an association between IL28B and treatment response in genotype 2/3 patients who did not achieve RVR but not in those who achieved RVR.[34]
Other studies of IL28B polymorphisms in HCV genotypes 2 and 3 have produced mixed results. Rauch et al found no significant impact of host IL28B genotype on treatment response in HCV genotype 2/3 patients when compared with HCV genotype 1 or 4 patients.[26] These findings were also seen by Rallón et al in patients co-infected with, human immunodeficiency virus (HIV) and HCV genotype 3.[35] Moghaddam et al have shown that polymorphisms near the IL28B gene show association with rapid viral response but not sustained viral response to PEG-IFN/RBV therapy in HCV genotype 3-infected patients.[36] Stattermayer et al have shown that in contrast to genotypes 1 and 4, the IL28 gene polymorphisms had no impact on SVR rates in genotype 2/3.[33] However, recent other studies from Germany, Taiwan, and Japan have shown association of IL28B genotype with SVR.[37–39]

(b) The value of IL28B polymorphisms testing in this population may be for patients who do not

achieve RVR: Mangiaet al did not find any association of IL28B polymorphisms with SVR in patients with genotype 2/3 who achieved RVR.[34] However, there was a strong association between IL28B and treatment response only among the subjects who did not achieve a rapid virologic response. Their data suggested that analysis of IL28B genotype might be used to guide treatment for these patients.

(c) **There may be a gene dose effect with heterozygotes having an intermediate SVR between homozygotes for favorable or unfavorable genotypes.[34]**

(d) **There may be intersubgenotypic differences between genotypes 2a and 2b patients infected with HCV** with genotype 2b showing lower response rates and IL28B polymorphism being predictive of treatment outcomes, especially with genotype 2b.[40]

(e) **The C/C genotype of rs12979860 may be overrepresented among patients infected with viral genotypes non-1[41]:** The effect of IL28B gene polymorphisms on treatment response may be attenuated in genotypes 2 and 3. These patients are generally easily treated, and hence, the IL28B polymorphisms may have a limited impact on the SVR. However, in patients who do not achieve an RVR, IL28B gene polymorphisms may have a role.

Interleukin 28B Polymorphisms and Spontaneous Clearance of Hepatitis C Virus

One-third of patients with exposure to HCV are able to spontaneously clear the virus. Thomas et al were the first to demonstrate the association of IL28B polymorphism with resolution of acute HCV infection.[42] They showed that the rs12979860 polymorphism had a marked impact on natural clearance of HCV. They genotyped 1008 patients from 6 separate HCV cohorts and compared individuals who cleared the virus spontaneously (n=388) with those with persistent infection (n=620). Patients with the C/C genotype at rs12979860 were 3 times more likely to spontaneously clear HCV relative to patients with T/T and C/T genotypes combined (odds ratio [OR]=0.33, $p<10^{-12}$). Similar data were reported from Spain by Montes-Cano et al.[41] Tillman et al evaluated the role of the rs12979860 polymorphism in a cohort of German women who had received anti-D immunoglobulin contaminated with HCV genotype 1b three decades earlier from 1978 to 1979.[43] They found that spontaneous viral clearance was seen in 6% of T/T homozygotes, 24% of C/T heterozygotes, and 64% of C/C homozygotes.

Rauch et al reported that the SNP rs809917 was associated with spontaneous clearance of HCV in Swiss individuals.[26]

While the above studies were retrospective, Grebely et al, in a prospective study, showed that genetic variations in IL28B gene was associated with spontaneous HCV clearance in recently acquired infection.[44] Homozygosity at the SNP rs8099917 (T/T vs G/T or G/G) was the only factor independently predictive of time to spontaneous clearance. They also found that acute symptomatic illness with jaundice was greater among T/T homozygotes compared with other genotypes (32% vs 5%, p=0.047). However, unlike in chronic infection, genetic variation in the IL28B gene did not impact response to treatment during recent HCV infection. The absence of an observed effect of IL28B and response to treatment for early HCV infection are not surprising, given the higher SVR observed during PEG-IFN treatment for acute HCV infection when compared with chronic infection.[45–47] The authors propose that individuals with unfavorable IL28B genotype (rs8099917 G/G or G/T) could be more strongly recommended for early therapeutic intervention for acute HCV infection, given their low likelihood of spontaneous clearance, but IFN-based therapeutic outcome was not compromised.

The IL28B gene encodes IFN-λ3, which is involved in the early host innate immune response to HCV, and may explain the observed effect on spontaneous clearance.[48]

Other Emerging Data of Interleukin 28B Polymorphisms and Hepatitis C Virus

Workers have reported the value of IL28B gene polymorphisms in response to HCV therapy in the setting of HIV/HCV co-infection.[35,49] In patients with recurrent HCV after orthotopic liver transplantation, IL28B polymorphisms allow prediction of SVR to PEG-IFN/RBV therapy.[50,51] The value of IL28B polymorphisms have also been shown to predict response to triple therapy, including the directly acting antiviral drug telaprevir along with PEG-IFN/RBV.[52]

Translating the Association into Clinical Decision Making

The association of IL28B gene polymorphisms on the natural history and response to treatment of HCV has a potential to impact decision making in acute and chronic HCV infection. The natural history of hepatitis C infection based on IL28B polymorphism haplotype is depicted in Figure 1.

Acute Hepatitis C

In those who do not appear to be recovering within 2–4 months after onset of the disease, antiviral treatment should be considered, as a high percentage of patients (>80–90%) may respond, and the risk of chronic disease is high.[53]

It has also been suggested to follow up these patients with HCV RNA quantification every 4 weeks and to treat only those still positive at 12 weeks after initial presentation.[54] Some clinicians may prefer to start treatment earlier if the HCV RNA is high and not declining. With IL28B gene polymorphisms having been reported to

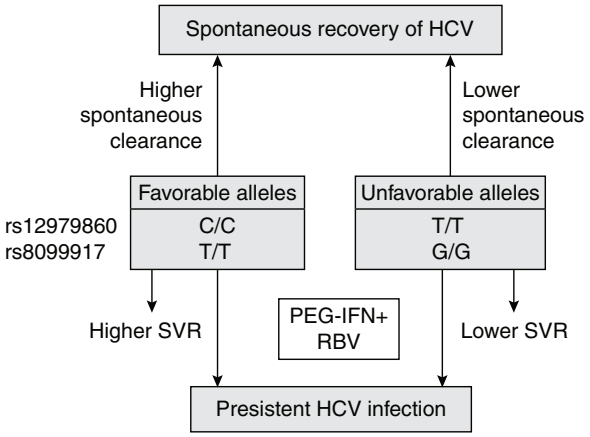
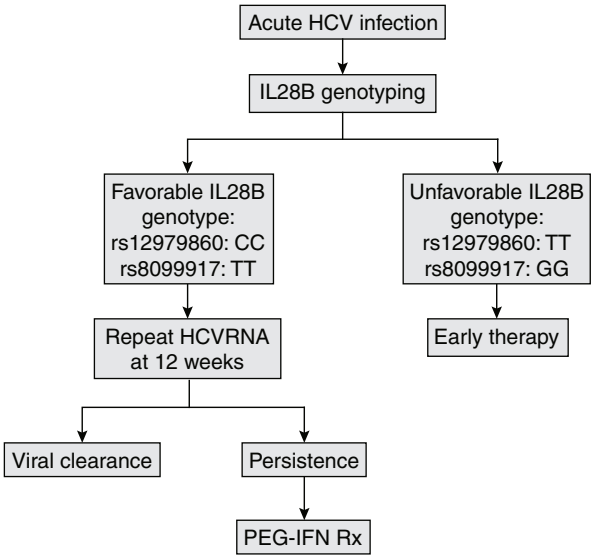
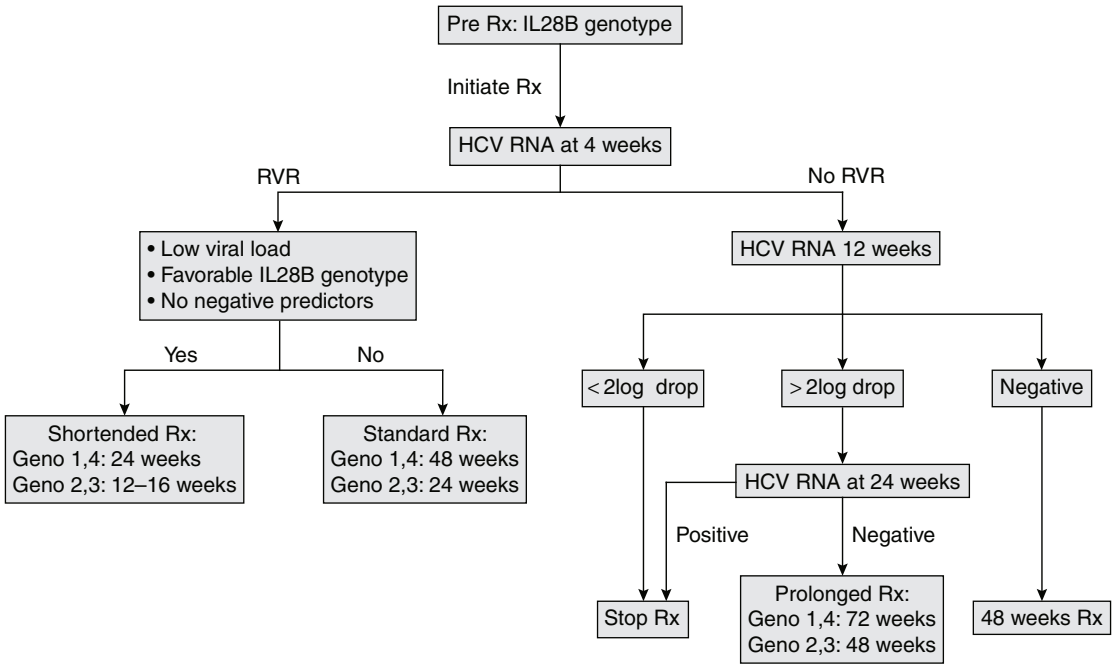


Figure 1 Natural history of hepatitis C infection based on IL28B polymorphism haplotype.
HCV: hepatitis C virus, SVR: sustained virological response, PEG-IFN+ RBV: pegylated interferon and ribavirin.



Algorithm 1 Proposed algorithm for management of acute hepatitis C virusinfection using IL28B genotype testing.
HCV: hepatitis C virus, IL28B: interleukin 28B, RNA: ribonucleic acid, PEG-IFN: pegylated interferon.



Algorithm 2 Proposed algorithm for incorporation of IL28B genetic testing along with viral kinetics into the clinical management of chronic hepatitis C virus infection.
IL28B: interleukin 28B, HCV: hepatitis C virus, RNA: ribonucleic acid.

The definitions of virological response are as below:

Rapid virological response (RVR): Undetectable HCV RNA in a sensitive assay (lower limit of detection 50 IU/mL) at week 4 of therapy, maintained up to end of treatment.

Early virological response (EVR): HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment.

Delayed virological response (DVR): >2$\log_{10}$ drop but detectable HCV RNA at week 12, HCV RNA undetectable at week 24, maintained up to end of treatment.

Partial non-response (PR): >2$\log_{10}$ IU/mL decrease in HCV RNA level from baseline at 12 weeks of therapy but detectable HCV RNA at weeks 12 and 24.

Sustained virological response (SVR): Undetectable HCV RNA level (<50 IU/mL) 24 weeks after treatment.[53]

predict clearance of HCVRNA in acute infection, it has been suggested that IL28B gene testing be incorporated in decision making to decide upon the initiation of therapy.[45,55] A proposed algorithm of management of acute HCV infection incorporating IL28B gene testing is presented (Algorithm 1).

Chronic Hepatitis C

The IL-28B polymorphism test may guide the management of newly acquired HCV infection. A suggested clinical algorithm for incorporation of IL28B genetic testing along with viral kinetics into the clinical management of chronic HCV infection is presented (Algorithm 2). Patients with RVR with low viral load, no negative predictors, and a favorable genotype may be considered for abbreviated therapy. For patients who do not achieve RVR, further therapy would be decided based on subsequent viral kinetics.

CONCLUSION

The identification of IL28B gene polymorphisms as a predictor of response to therapy in HCV is an exciting development in the management of HCV. It is likely that the IL28B status may eventually be used to personalize the duration of therapy with PEG-IFN/RBV. However, in easy to treat cases like genotype 2/3 patients who achieve RVR or in treatment initiated in acute HCV, it appears that IL28B testing may have less clinical utility. This raises questions about justifying the cost of incorporating IL28B testing in routine practice in a population where the majority of HCV infections are of genotype 2/3. More studies will also be required of the role of IL28B genotype in the era of direct antivirals, which rapidly reduce the viral load and may therefore diminish the influence of IL28B genotyping in predicting SVR. The effect of the IL28B genotype, however, is not absolute, and it should not be used as a criterion for denying therapy to a person with an unfavorable IL28B genotype.

REFERENCES

1. Lavanchy D. The global burden of hepatitis. *Liver International* 2009;29:74–81.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. AASLD practice guidelines—diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335–74.
3. Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis* 2005;9:383–98.
4. Strader DB, Seeff LB. The natural history of chronic hepatitis C infection. *Eur J Gastroenterol Hepatol* 1996;8:324–8.
5. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *Hepatology* 2002;36(Suppl):S1–2.
6. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36(Suppl):S35–46.
7. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 2000;132:296–305.
8. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463–72.
9. National Institutes of Health Consensus Development Conference Panel statement. Management of hepatitis C. *Hepatology* 1997; 26:2S–11.
10. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001;358:958–65.
11. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–82.
12. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346–55.
13. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006; 131:470–7.
14. Muir AJ, Bornstein JD, Killenberg PG; Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and RBV for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004;350:2265–71.
15. Attia J, Ioannidis JP, Thakkinstian A, et al. How to use an article about genetic association: a background concepts. *JAMA* 2009; 301:74–81.
16. Clark PJ, Thompson AJ, McHutchison JG. IL28B genomic-based treatment paradigms for patients with chronic hepatitis C infection: the future of personalized HCV therapies. *Am J Gastroenterol* 2011;106:38–45.
17. Thio CL. Host genetic factors and antiviral immune responses to hepatitis C virus. *Clin Liver Dis* 2008;12:713–26.
18. Rauch A, Gaudieri S, Thio C, Bochud PY. Host genetic determinants of spontaneous hepatitis C clearance. *Pharmacogenomics* 2009;10:1819–37.
19. Little J, Higgins JP, Ioannidis JP, et al. STrengthening the REporting of Genetic Association studies (STREGA)—an extension of the STROBE statement. *Eur J Clin Invest* 2009;39:247–66.
20. Asselah T, Bieche I, Paradis V, Bedossa P, Vidaud M, Marcellin P. Genetics, genomics, and proteomics: implications for the diagnosis and the treatment of chronic hepatitis C. *Semin Liver Dis* 2007;27:13–27.
21. Rauch A, Rohrbach J, Bochud PY. The recent breakthroughs in the understanding of host genomics in hepatitis C. *Eur J Clin Invest* 2010;40:950–9.
22. Ahlenstiel G, Booth DR, George J. IL28B in hepatitis C virus infection: translating pharmacogenomics into clinical practice. *J Gastroenterology* 2010;45:903–10.
23. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461:399–401.
24. 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;41:1105–9.
25. 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;41:1100–4.
26. Rauch A, Kutalik Z, Descombes P, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010;138: 1338–45.
27. Romero-Gomez M, Eslam M, Ruiz A, Maraver M. Genes and hepatitis C: susceptibility, fibrosis progression and response to treatment. *Liver International* 2011;31:443–60.

28. Aghemo A, Colombo M. Genetic variation in interleukin-28B predicts hepatitis C treatment-induced viral clearance in genotype 1 patients: the dawn of a new era. *Gastroenterology* 2010;138:2546–9.
29. Asrani SK, Kim WR. Predicting response to pegylated interferon/ribavirin-based therapy in genotype 1 chronic hepatitis C patients: results of 3 independent genome-wide association studies. *Gastroenterology* 2010;138:1622–4.
30. Shackel NA, Bowen DG, McCaughan GW. Snipping away at hepatitis C. *Hepatology* 2010;51:703–5.
31. Iadonato SP, Katze MG. Genomics: hepatitis C virus gets personal. *Nature* 2009;461:357–8.
32. Li S, Hu P, Zhang QQ, et al. Single nucleotide polymorphisms of the IL28B and sustained virologic response of patients with chronic hepatitis C to PEG-interferon/ribavirin therapy: a meta-analysis. *Hepatol Mon* 2011;11:163–72.
33. Stattermayer AF, Stauber R, Hofer H, Rutter K, Beinhardt S, Scherzer TM. Impact of IL28B genotype on the early and sustained virological response in treatment-naïve patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011;9:344–50.
34. Mangia A, Thompson AJ, Santoro R, et al. IL28B polymorphism determines treatment response of patients with hepatitis C genotypes 2 or 3 who do not achieve a rapid virologic response. *Gastroenterology* 2010;139:821–7.
35. Rallón NI, Naggie S, Benito JM, et al. Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. *AIDS* 2010;24:F23–9.
36. Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. *Hepatology* 2011;53:746–54.
37. Sazzarin C, Susser S, Doehring A, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol* 2011;54:415–21.
38. Yu ML, Huang CF, Huang JF, et al. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology* 2011;53:7–13.
39. Kawaoka T, Hayes CN, Ohishi W, et al. Predictive value of the IL28B polymorphisms on the effect of interferon therapy in chronic hepatitis C patients with genotype 2a and 2b. *J Hepatol* 2011;54:408–14.
40. Sakamoto N, Nakagawa M, Tanaka Y, et al. Association of IL28B variants with response to pegylated-interferon alpha plus ribavirin combination therapy reveals intersubgenotypic differences between genotypes 2a and 2b. *J Med Virol* 2011;83:871–8.
41. Montes-Cano MA, Garcıa-Lozano JR, Abad-Molina C, et al. Interleukin-28B genetic variants and hepatitis virus infection by different viral genotypes. *Hepatology* 2010;52:33–7.
42. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; 461:798–801.
43. Tillman HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance, of acute hepatitis C virus and jaundice. *Gastroenterology* 2010;139:1586–92.
44. Grebely J, Petoumenos K, Hellard M, et al. Potential role for IL28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology* 2010;52:1216–24.
45. Wiegand J, Buggisch P, Boecher W, et al. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology* 2006;43:250–6.
46. Kamal SM, Ismail A, Graham CS, et al. Pegylated interferon alpha therapy in acute hepatitis C: relation to hepatitis C virus-specific T cell response kinetics. *Hepatology* 2004;39:1721–31.
47. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001;345: 1452–7.
48. Marcello T, Grakoui A, Barba-Spaeth G, et al. Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology* 2006;131:1887–98.
49. Pineda JA, Caruz A, Rivero A, et al. Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfected with HIV and hepatitis C virus. *Clin Infect Dis* 2010; 51:788–95.
50. Fukhara T, Taketomi A, Motomura T, et al. Variants in IL28B in liver recepients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. *Gastroenterology* 2010;139:1577–85.
51. Guillouche P, Feray C. Systematic review: anti-viral therapy of recurrent hepatitis C after liver transplantation. *Aliment Pharmacol Ther* 2011;33:163–74.
52. 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;52:421–9.
53. Craxì A, Pawlotsky JM, Wedemeyer H, et al. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011 Feb 28. [Epub ahead of print]
54. Hofer H, Watkins-Riedel T, Janata O, Penner E, Gangl A, Ferenci P. Spontaneous viral clearance in patients with acute hepatitis C: predictability by repeated measurements of serum HCV concentration. *Hepatology* 2002;36:286A.
55. Perlman BL. The Il28B genotype: how will it affect the care of patients with hepatitis C virus infection? *Curr Gastroenterol Rep* 2011;13:78–86.