

IL-28B As a Predictor of Sustained Virologic Response in Patients with Chronic Hepatitis C Virus Infection

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Abstract: Genome-wide association studies have recently identified single nucleotide polymorphisms in proximity to the interleukin-28B (*IL-28B*) gene that can predict sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection who are undergoing therapy with pegylated interferon (IFN) α and ribavirin. *IL-28B* encodes IFN- λ 3, a type III IFN involved in host antiviral immunity. Favorable variants of the 2 most widely studied *IL-28B* polymorphisms, rs12979860 and rs8099917, are strong pretreatment predictors of early viral clearance and SVR in patients with genotype 1 HCV infection. Variations in the distribution of *IL-28B* alleles may partly explain differences in SVR rates among ethnic groups. Further investigations have implicated *IL-28B* in the development of chronic HCV infection versus spontaneous resolution of acute infection and suggest that *IL-28B* may be a key factor involved in host immunity against HCV. Clinical trials of IFN- λ as a therapeutic agent for chronic HCV infection are currently underway. The use of *IL-28B* polymorphisms as a predictive tool will have a major impact on treatment strategies for chronic HCV infection, particularly in the context of emerging therapies and direct-acting antiviral agents.

Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States, affecting over 4 million people and accounting for the majority of newly diagnosed cases of chronic liver disease.^{1,2} Advanced liver disease resulting from chronic HCV infection is a major cause of liver-related mortality and is expected to increase in prevalence over the next decade.^{3,4} Pegylated interferon (pegIFN) α -2a or pegIFN α -2b in combination with ribavirin (RBV) was the standard-of-care treatment for chronic hepatitis C—prior to the recent licensure of boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex) in the United States—and sustained virologic response (SVR) occurred in only approximately half of patients.⁵⁻⁸

Keywords

Chronic hepatitis C virus, genetic, genome, *IL-28B*, interferon lambda, pegylated interferon, ribavirin, sustained virologic response

The ability to predict treatment outcomes is an important consideration in the management of chronic HCV infection, as the approach to treatment has become more individualized in order to achieve optimal tolerability, duration of therapy, and virologic response. HCV genotype is well established as the strongest predictor of treatment response and is a primary determinant of treatment duration and RBV dose.⁷ Other host and viral factors have been identified as predictors of a poor response to therapy; these factors include high serum HCV RNA levels, advanced hepatic fibrosis, increased age, obesity, and black race.⁵⁻⁹

A major unresolved question is the extent to which host genetic factors may influence response to antiviral therapy in patients with chronic HCV infection and whether reliable genetic markers predictive of SVR can be identified. As knowledge of the human genome has expanded and our ability to detect genomic differences among individuals has become more advanced, recent studies have identified single nucleotide polymorphisms (SNPs) in proximity to the interleukin-28B (*IL-28B*) gene as important predictors of treatment outcome. These findings have not only provided a new window into host responsiveness to IFN-based therapy but have also yielded insights into genetic susceptibility to chronic HCV infection, the molecular biology of host immunity against HCV, and the potential for discovery of new therapeutic agents.

Discovery of *IL-28B* Polymorphisms

The recent development of genome-wide association studies (GWAS) has made possible the ability to efficiently identify genomic variations among individuals on a large scale.¹⁰ These studies involve techniques that allow investigators to survey the entire genome and identify SNPs that link groups of individuals with complex traits, such as response to antiviral therapy. Four recently published GWAS have investigated the genetic predictors associated with SVR in patients with genotype 1 HCV infection.¹¹⁻¹⁴ These GWAS were performed in distinct populations, but all 4 studies identified SNPs located on chromosome 19 in the region of the *IL-28B* gene as the strongest predictors of virologic response.

The first and largest of these studies arose from the IDEAL study, in which 1,137 patients were included in a genome-wide association study.¹¹ The IDEAL study was a large, randomized, controlled trial of over 3,000 patients that investigated different dosing regimens of pegIFN α -2b and pegIFN α -2a in combination with RBV.⁸ A study of patients in the IDEAL trial who consented to undergo a genome-wide association study showed a significantly increased likelihood of SVR in

association with the C/C genotype of the rs12979860 SNP, which is located 3 kb upstream of the *IL-28B* gene (Figure 1). Three smaller studies involving Japanese, Australian, and European cohorts all reported increased SVR rates in patients with the T/T genotype of another SNP, rs8099917, which is located 8.9 kb downstream from *IL-28B* in the intergenic region between the *IL-28A* and *IL-28B* genes.¹²⁻¹⁴

Subsequent studies investigating both the rs12979860 and rs8099917 SNPs have confirmed these findings. The *IL-28A* and *IL-28B* genes encode IFN- λ 2 and IFN- λ 3, respectively, both of which are cytokines in the IFN- λ family.¹⁵ The discovery of *IL-28B* in association with virologic response has many implications, particularly in relation to the role that IFN- λ plays in host immunity and clearance of HCV.¹⁶

Sustained Virologic Response

Genotype 1

The predictive value of genetic markers has the greatest potential impact in patients with genotype 1 infection who are undergoing antiviral therapy with pegIFN and RBV for chronic HCV infection, as this group has lower rates of SVR.⁵⁻⁸ As new and more effective antiviral therapy becomes available, a better understanding of an individual's potential for virologic response may influence the decision of whether to initiate antiviral therapy, which antiviral agents to choose, and how long to continue therapy.¹⁷⁻¹⁹ Given the challenges associated with optimizing treatment outcomes in patients with chronic genotype 1 HCV infection, much of the data on *IL-28B* as a predictor of SVR involves this population.

The first published genome-wide association study of *IL-28B* as a predictor of SVR, reported by Ge and colleagues, included only genotype 1–infected patients.¹¹ Most of these patients were enrolled in the IDEAL study, but this study also included a small subset of patients from another prospective clinical trial.¹¹ In addition to its large size, another major advantage of this study was its diversity: One quarter of these patients were either black or Hispanic. Overall, patients with the C/C genotype of the rs12979860 polymorphism had a 2-fold higher rate of SVR compared to patients with the T/T genotype (Figure 1). This relationship was consistent across different ethnic groups and was later confirmed through an intention-to-treat analysis that included all members of this cohort, regardless of adherence (Figure 2).²⁰ In addition, the C/C genotype was found to be the strongest predictor of SVR, independent of serum HCV RNA level, fibrosis stage, or ethnicity.^{11,20} Subsequent studies in European and American cohorts demonstrated a stronger association between SVR rates and the C/C genotype of

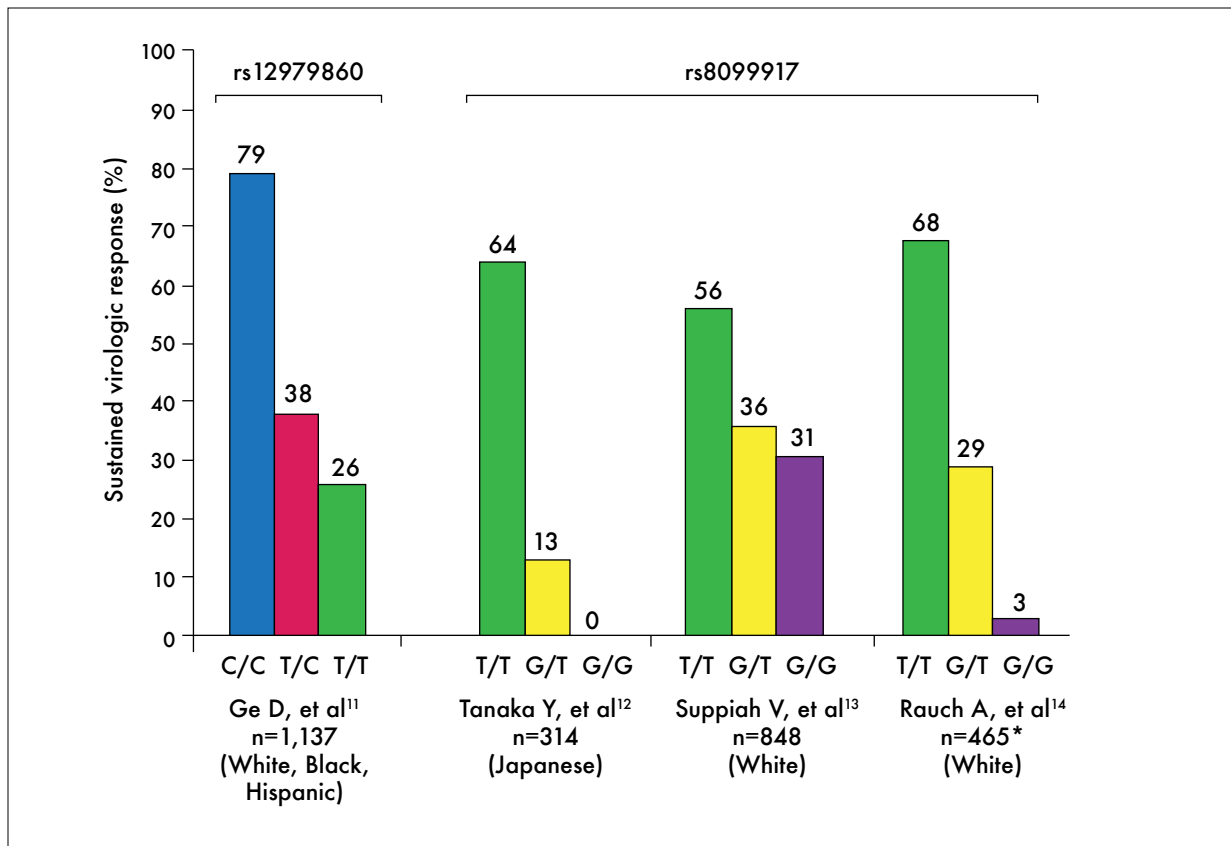


Figure 1. This graph shows rates of sustained virologic response (SVR) based on interleukin-28B single nucleotide polymorphism genotypes as reported by 4 genome-wide association studies of patients who underwent antiviral therapy with combination pegylated interferon α and ribavirin. The C/C variant of the rs12979860 polymorphism and the T/T variant of the rs8099917 polymorphism are associated with an increased likelihood of SVR.

*Approximately one half of patients from the study by Rauch and colleagues were infected with genotype 2 or 3 hepatitis C virus (HCV) infection, while the other studies included only patients with genotype 1 HCV infection.¹¹⁻¹⁴

rs12979860, compared to variants that carry the T allele, such that the T allele was found to be an independent predictor of treatment failure.^{21,22}

Additional GWAS identified a second SNP, rs8099917, as a predictor of virologic response in patients with genotype 1 HCV infection. In a Japanese cohort, Tanaka and colleagues reported that rs8099917 had a strong association with response to therapy and that the presence of the G allele was the most significant independent predictor of null response.¹² Likewise, the T/T genotype of the rs8099917 polymorphism was associated with a high SVR rate (Figure 1). Suppiah and colleagues also identified rs8099917 as being strongly associated with virologic response; this association was seen in an initial group of Australian patients and was then validated in a larger cohort that included Europeans.¹³ Similar to the Tanaka study, the Suppiah study reported the highest rate of SVR in patients with the T/T genotype of rs8099917, while the presence of the

G allele was predictive of nonresponse.^{12,13} In both of these studies, the association between rs8099917 and SVR was independent of serum HCV RNA level, fibrosis stage, or gender.^{12,13} A more recent Swiss genome-wide association study also found the presence of the G allele to be strongly associated with treatment failure.¹⁴ Additional reports have validated these findings, including a Japanese study in which the T/T genotype of rs8099917 was found to be the strongest independent predictor of SVR, whereas the G allele was the strongest independent predictor of null virologic response in multivariate analyses.²³

At this time, only limited preliminary data are available on *IL-28B* as a predictor of SVR in patients with chronic genotype 1 HCV infection who receive triple therapy consisting of pegIFN and RBV plus either telaprevir or boceprevir.²⁴⁻²⁶ In a small study from Japan, treatment-naïve patients and prior nonresponders were treated with a 12-week regimen of triple therapy that included telaprevir (with or without an additional 12 weeks of

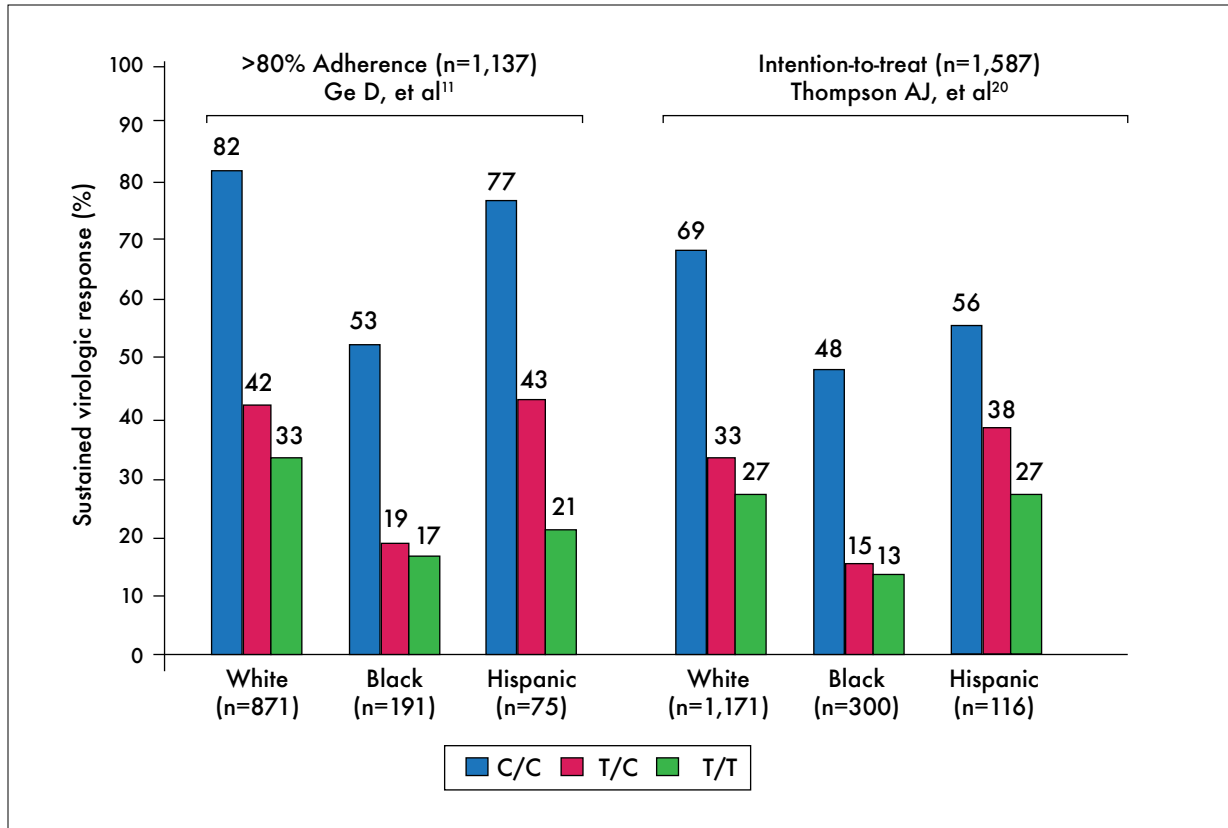


Figure 2. Sustained virologic response (SVR) rates based on rs12979860 polymorphism genotypes differ across ethnic groups. This graph shows SVR rates for both the adherent and intention-to-treat cohorts of the genome-wide association study that was conducted among patients enrolled in the IDEAL study. The C/C variant was most strongly associated with SVR, independent of ethnicity or adherence.

dual therapy with pegIFN and RBV), and increased SVR rates were noted in patients with favorable rs12979860 and rs8099917 genotypes.²⁴ In a larger phase III study, the impact of rs12979860 genotypes on SVR rates was retrospectively assessed in 527 of 662 patients enrolled in a pivotal study of telaprevir administered in combination with pegIFN and RBV in patients with prior treatment failure.²⁵ The highest proportion of rs12979860 T/T genotype was observed in prior null responders (28%), while the highest frequency of the C/C genotype occurred among relapsers (27%). In the overall population of prior relapsers, partial responders, and null responders who were treated with triple therapy, SVR rates were 79% in patients with the C/C genotype, 60% with the T/C genotype, and 61% with the T/T genotype. However, *IL-28B* genotype did not predict outcomes in the individual groups based on prior treatment response. In pivotal trials of triple therapy involving boceprevir plus pegIFN and RBV, rs12979860 genotype was a strong predictor of SVR in both treatment-naïve and non-responder cohorts, although virologic response at Week 4

was a stronger predictor than *IL-28B* genotype or other baseline variables.²⁶

Another challenging population in which virologic response to therapy is decreased includes patients with chronic hepatitis C who are co-infected with HIV. Data have emerged suggesting that rs12979860 and rs8099917 *IL-28B* polymorphisms may play an important role in predicting SVR in this population as well. Several studies involving European cohorts have reported the rs12979860 C/C and rs8099917 T/T variants to be independent predictors of SVR in patients with HCV/HIV co-infection, particularly in patients with genotype 1 HCV infection.²⁷⁻²⁹

Genotypes 2 and 3

In contrast to the data on genotype 1 HCV infection, the available data on *IL-28B* polymorphisms as predictors of SVR in patients with genotype 2 or 3 HCV infection are conflicting. However, *IL-28B* may play a role in some patients, particularly those who do not demonstrate a rapid virologic response (RVR), which is

defined by undetectable levels of HCV RNA in serum at 4 weeks of therapy. Several studies, including 1 of the initial GWAS that identified rs8099917 as a predictor of SVR in patients with genotype 1 HCV infection, have not demonstrated any clear association between *IL-28B* polymorphisms and SVR in patients with genotype 2 or 3 HCV infection.^{14,21,30} Some reports have identified favorable variants of both rs8099917 and rs12979860 as being independently associated with RVR but not SVR, suggesting an increased rate of relapse in this subset of patients.^{31,32}

In contrast, 2 European studies found an association between the C/C variant of rs12979860 and SVR in cohorts with genotype 2 or 3 HCV infection, although this relationship may be strongest in patients who do not achieve RVR.^{33,34} Ultimately, given that overall rates of SVR are significantly higher in patients with genotype 2 or 3 HCV infection compared to patients with genotype 1 HCV infection, the role of predictive factors such as *IL-28B* polymorphisms may not be as important in the former group.

Early Viral Clearance

The most important predictive factor during a course of antiviral therapy is the change in serum HCV RNA level, with clearance of HCV earlier during therapy being strongly predictive of SVR. RVR has a positive predictive value for SVR of up to 90% in patients with genotype 1 HCV infection, while failure to achieve an early virologic response (EVR; defined as a greater-than-2-log₁₀ decrease in HCV RNA level at Week 12 of therapy) has a negative predictive value for SVR of up to 100%.^{6,35,36}

Several reports in different populations have shown that *IL-28B* polymorphisms are also predictive of these parameters. Studies evaluating early viral kinetics during therapy have observed that patients with the rs12979860 C/C genotype have significantly faster first-phase declines in serum HCV RNA levels during the first 24 hours following initiation of therapy.^{21,37} Likewise, achievement of RVR has been strongly associated with the rs12979860 C/C genotype as well as the T/T genotype of the rs8099917 polymorphism.^{20,21,23} These *IL-28B* profiles are also associated with achievement of complete EVR, with undetectable levels of HCV RNA at Week 12, independent of ethnicity.^{20,23}

Role of *IL-28B* Polymorphisms in Liver Transplantation

IL-28B polymorphisms may play an important role in patients with chronic HCV infection and end-stage liver disease who undergo liver transplantation. Recurrence of HCV infection occurs in all liver transplant recipients

with detectable HCV RNA levels at the time of transplantation, resulting in chronic hepatitis, progressive fibrosis, and cirrhosis in up to 30% of patients.³⁸ Recent data reveal that *IL-28B* polymorphisms may predict both recurrence of disease and response to antiviral therapy following liver transplantation.

A study assessing both recipient and donor *IL-28B* rs12979860 genotypes in consecutive HCV-infected patients undergoing liver transplantation found that the presence of the recipient C allele was an independent predictor of delayed recurrence of disease at 2 and 5 years.³⁹ Both recipient and donor C/C genotypes appear to be strongly associated with SVR, although 1 recent study suggested that the donor genotype may be more important in this setting.^{39,40}

Mechanisms and Immunology

Epidemiology

An important finding associated with the *IL-28B* rs12979860 polymorphism is the distribution of alleles across different ethnic groups. Ge and colleagues reported the highest frequency of the C allele in East Asians, followed by Americans of European ancestry and Hispanics; the lowest frequency of the C allele was found in blacks.¹¹ In a further analysis of the intention-to-treat population, the C/C genotype was more prevalent in whites and Hispanics, while the T/T genotype was most common in blacks (Figure 3).²⁰ Ge and colleagues proposed that possibly one half of the difference in SVR rates between whites and blacks could be accounted for by differences in C allele frequency.¹¹

A large, population-based study of over 2,000 individuals from different areas of the world revealed that the C allele occurred with the highest frequency in areas of East Asia, followed by Europe and then Africa.⁴¹ The predictive value of the C/C genotype may also vary across different ethnic groups, as the presence of a C/C genotype appears to have a greater specificity and negative predictive value for SVR in blacks than in whites or Hispanics (Table 1).²⁰

Association with Spontaneous Viral Clearance

Findings from the initial genome-wide association study suggested that *IL-28B* may play a role in determining whether acute HCV infection leads to spontaneous clearance or chronic infection. Ge and colleagues first noted that the presence of the C allele (rs12979860) was lower in patients with chronic genotype 1 HCV infection compared to matched healthy controls, suggesting that the C allele may be associated with spontaneous resolution.¹¹ The same finding has been noted in additional studies, including a large study of over 1,000 individuals in which the prevalence of the rs12979860 genotype

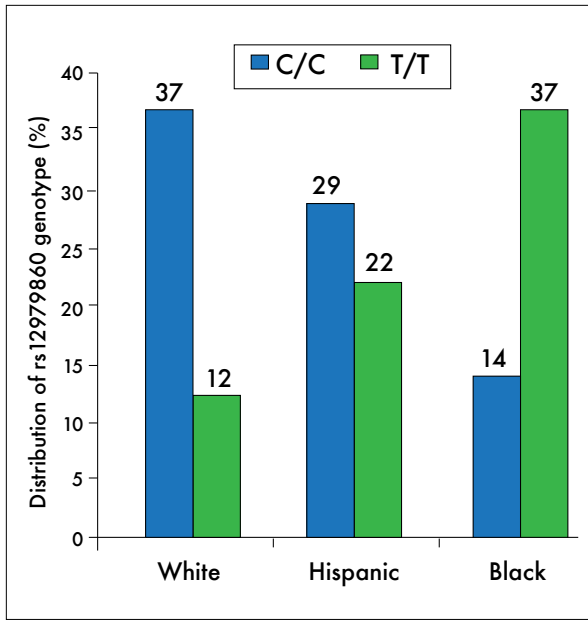


Figure 3. The relative distribution of interleukin-28B rs12979860 polymorphism genotypes varies among different ethnic groups. This graph shows the distribution of alleles associated with the rs12979860 polymorphism across different ethnic backgrounds, with specific attention to the C/C and T/T genotypes. Data were obtained from a large multiethnic cohort with genotype 1 hepatitis C virus infection, based on an intention-to-treat analysis.

Adapted from Thompson AJ, et al.²⁰

was investigated in patients who achieved spontaneous resolution and those who developed chronic HCV infection.^{30,41} This study found that the C allele occurred more frequently in patients who spontaneously cleared HCV. Individuals with the C/C genotype had a 3-fold

greater likelihood of spontaneous HCV clearance compared to patients who had the T/C or T/T genotype. Additionally, the strong association between C/C genotype and spontaneous clearance was present in both whites and blacks.

A recent German cohort study reported similar findings: The C/C genotype was associated with the greatest likelihood of spontaneous clearance, followed by the T/C genotype at an intermediate rate, and then the T/T genotype with the lowest likelihood of clearance.⁴² Interestingly, patients with the C/C variant were more likely to have acute jaundice, although the positive association between jaundice and spontaneous clearance was more significant in those with non-C/C genotypes. Similar findings have been reported in association with the rs8099917 polymorphism, in which the favorable T/T genotype is associated with spontaneous resolution; this relationship was also found in HCV/HIV co-infected individuals.^{14,43}

The distribution of *IL-28B* polymorphisms may also vary among HCV genotypes, suggesting further differences in the risk of developing a chronic infection. Studies have shown that the C/C variant occurs in a higher proportion of patients with genotype 2 or 3 HCV infection compared to patients with genotype 1 HCV infection.^{22,30} When compared with healthy controls, the frequency of the C/C genotype appears to be highest in controls, intermediate in patients with genotype 2 or 3 HCV infection, and lowest in patients with genotype 1 HCV infection.³⁴ These findings suggest a potentially increased rate of spontaneous clearance in patients infected with genotype 2 or 3 HCV compared to genotype 1 HCV. However, further studies will be required to determine the clinical relevance of these observations and to ascertain whether these findings bear any relationship to differences in rates of response to therapy among HCV genotypes.

Table 1. Performance Characteristics of Interleukin-28B Polymorphisms in the Prediction of Sustained Virologic Response

	Sensitivity	Specificity	PPV	NPV
C/C (rs12979860)				
Stättermayer AF, et al ^{21*}	0.50	0.86	0.81	0.59
Thompson AJ, et al ^{20†}				
White	0.56	0.79	0.69	0.68
Black	0.35	0.91	0.48	0.86
Hispanic	0.40	0.78	0.56	0.66
McCarthy JJ, et al ^{22*}	0.64	0.77	—	—
T/T (rs8099917)				
Stättermayer AF, et al ^{21*}	0.68	0.62	0.72	0.58

*Included patients with both genotype 1 and non-genotype 1 hepatitis C virus infection.

†Included only patients with genotype 1 hepatitis C virus infection.

NPV=negative predictive value; PPV=positive predictive value.

Interferon- λ and Hepatitis C Virus Infection

The IFN- λ cytokine family includes IFN- λ 1, IFN- λ 2, and IFN- λ 3, which are encoded by the *IL-29*, *IL-28A*, and *IL-28B* genes, respectively.¹⁵ The IFN- λ cytokines are considered to be type III IFNs; similar to type I IFNs, they are involved in the host response to viral infection. The strong association between *IL-28B* polymorphisms and response to antiviral therapy in patients with chronic HCV infection has led to a greater understanding of the role that IFN- λ plays in immune-mediated and treatment-associated clearance of HCV. *IL-28B* appears to be uniquely important in response to HCV therapy, as GWAS have not reported any SNPs outside of the *IL-28B* haplotype block or *IL-28A/B* locus that demonstrate a significant association with virologic response.^{13,14} Although patients with nonresponder alleles have been reported to have decreased whole blood expression of *IL-28A* and *IL-28B* and decreased peripheral blood mononuclear cell *IL-28* mRNA expression, the question remains how SNPs in the region of *IL-28B* may regulate IFN- λ cytokine activity or function.^{12,13,16}

A series of intracellular events are critically important for limiting HCV replication and activating the cellular immunity involved in the clearance of infected hepatocytes.⁴⁴ In response to HCV infection, the activation of cellular transcription factors promotes secretion of type I IFNs such as IFN- α and IFN- β . Binding of type I IFNs to hepatocyte receptors results in activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signal transduction pathway and subsequent production of IFN-stimulated genes (ISGs), inhibition of HCV replication, and priming of effector cells involved in HCV-specific host adaptive immunity.⁴⁴ This adaptive immune response, which is characterized by CD4-positive helper T cells and CD8-positive cytotoxic T cells, plays a critical role in eradicating HCV in the setting of acute infection and during treatment of chronic infection.⁴⁵⁻⁴⁸

Emerging data reveal that IFN- λ 3 (*IL-28B*) may inhibit HCV replication via the JAK-STAT pathway, leading to expression of ISGs in a manner similar to that seen with type I IFNs.⁴⁹ Recent evidence also suggests that the intrahepatic expression of ISGs may vary based on *IL-28B* genotype.⁵⁰ These findings suggest that IFN- λ cytokines may play an important role in clearance of HCV both in the acute setting and during antiviral therapy. The use of IFN- λ as a therapeutic agent for chronic HCV infection is currently being studied, and phase I clinical studies are underway.⁵¹

IL-28B and Treatment Strategies

IL-28B polymorphisms have been reported to be the strongest pretreatment predictors of SVR independent of

other host and viral factors, including ethnicity, presence of advanced fibrosis, gender, or HCV RNA level. *IL-28B* genotype may lack sufficient sensitivity and specificity as a predictor of SVR in some populations when used alone, but it will greatly contribute to assessing patient responsiveness to therapy when used in conjunction with other clinical predictors. Whether *IL-28B* will be instrumental in selecting individuals who may benefit from a shorter duration of therapy has yet to be determined.

As novel, more effective, direct-acting antiviral agents (DAAs) become available for the treatment of chronic HCV infection, *IL-28B* may play a role in selecting specific antiviral agents or deciding to treat patients with pegIFN and RBV alone. Overall, *IL-28B* will certainly remain a key factor in treatment algorithms and will be included as part of an individualized approach to HCV treatment. Ongoing clinical studies will further elucidate how genetic profiling with *IL-28B* will affect treatment strategies and decision-making, particularly in the context of emerging DAAs.

Summary

The discovery of *IL-28B* as a predictor of SVR in patients with genotype 1 HCV infection will have a lasting impact, particularly in the development of individualized treatment strategies, understanding of host molecular biology and determinants of immune-mediated viral clearance, and development of novel antiviral therapies. The strong associations between *IL-28B* polymorphism genotypes and SVR are consistent across different ethnic groups and populations. *IL-28B* will be utilized most in the setting of chronic genotype 1 HCV infection and will be particularly beneficial to patients with difficult-to-treat characteristics, in whom *IL-28B* genotype may guide decisions on whether to initiate therapy, how long to continue therapy, and which antiviral agents to use. How *IL-28B* genetic profiling will be used in the setting of DAA therapy has yet to be determined. Further investigations into the molecular biology of IFN- λ cytokines as they relate to HCV infection are ongoing, and the development of IFN- λ as a viable treatment alternative remains an exciting prospect.

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