Viral Hepatitis C Gets Personal – The Value of Human Genomics to Public Health

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Abstract

About 180 million people worldwide are chronically infected with hepatitis C virus (HCV), with 3–4 million newly infected each year. Only 15–25% of acute HCV infections clear spontaneously, and the remainder persists as chronic HCV infection. More than 350,000 people die every year from hepatitis C-related liver failure and cancer. There is currently no vaccine and the standard-of-care therapies – peg-interferon alpha (pegIFN) plus ribavirin (RBV) – are expensive and have serious side effects. Also, they may be effective in only 40–50% of patients infected with HCV genotype 1, the most common HCV genotype in the US. Interleukin 28B *(IL28B)* genotype was recently and convincingly associated with response to pegIFN and RBV therapy. It has emerged as a robust pretreatment predictor of sustained virological response (SVR, i.e. virologic clearance) to pegIFN and RBV as well as to new triple therapy regimens that include a direct-acting antiviral agent with pegIFN and RBV and increase SVR rates as much as 75% in patients infected with HCV genotype 1. Testing for *IL28B* genotype may contribute to clinical decision-making and could inform clinical guidelines and public health policies.

Keywords

Hepatitis C; Host genetic predisposition to disease; *IL28B* polymorphism; Interferon response

Introduction and Epidemiology

Hepatitis C is an infectious disease primarily affecting the liver caused by the hepatitis C virus (HCV). It can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness. HCV, a bloodborne pathogen endemic in most parts of the world, infects an estimated 180 million people worldwide and causes 3–4 million new infections annually [1]. Only 15–25% of acutely infected individuals spontaneously clear HCV, while the remainder progress to chronic HCV infection and are, therefore, at risk for cirrhosis and hepatocellular carcinoma. Despite the serious illness it can cause, hepatitis C infection is often asymptomatic for many years or decades. Hepatitis C has been called a 'silent epidemic'

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because most infected people are unaware that they have a serious and progressive chronic disease.

In the US, hepatitis C mortality has increased substantially since the 1990s. Despite small declines and leveling of incidence overall in recent years, reports of HCV infection are increasing in some areas of the US [2, 3]. Current trends in HCV infection include an apparent increase in young, often suburban heroin injection drug users, infections in nonhospital healthcare (clinic) settings, and sexual transmission among persons infected with human immunodeficiency virus (HIV) [4]. Approximately 25% of persons with HIV infection are coinfected with HCV; both infections are associated with injection drug use [5]. In the absence of increased screening and treatment, models project an additional 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma and USD 10.7 billion in direct medical expenditures for HCV from 2010 through 2019 [6, 7].

Hepatitis C infection has a great propensity to cause chronic hepatitis, which occurs in 70–80% of those acutely infected [8]. This often persists and slowly worsens over 10–20 years. After acute infection, only 15–25% of persons with normal immune status resolve their infection without sequelae. End-stage liver disease can also occur. In 10–20% of chronically infected persons, cirrhosis develops slowly over 20–30 years, and hepatocellular carcinoma develops in 1–5%. Progression to liver fibrosis, development of cirrhosis and subsequent mortality are associated with age at infection, duration of HCV infection, HCV genotype, HIV coinfection, alcohol use, and male sex [8].

Hepatitis C Virus

HCV is an enveloped RNA virus within the *Flaviviridae* family. Its genome consists of a positive-stranded RNA molecule (about 9.6 kb) that encodes a large poly-protein precursor (about 3,000 amino acids). This precursor protein is cleaved by host and viral proteinases to generate at least 10 proteins. These HCV proteins function in viral replication and affect a variety of host cellular functions [9].

The genome of HCV is highly mutable. Because HCV is an RNA virus and lacks efficient proofreading ability as it replicates, virions infecting humans undergo evolution with time, giving rise to the notion that HCV persists as a collection of virus quasispecies. By constant mutation in a hypervariable region of the genome coding for the envelope proteins, HCV escapes immune surveillance and elimination by the host. As a consequence, most HCV infected people develop chronic infection [9].

HCV is highly heterogeneous. Six major genotypes (numbered from 1–6) with several distinct subtypes have been identified throughout the world [10]. Genotypes 1a and 1b are found worldwide and cause approximately 60% of all cases of infection. This diversity has distinct consequences: different genotypes vary in their responsiveness to treatment (see below) and their propensity to cause insulin resistance, steatosis, and progression to cirrhosis, fibrosis and hepatocellular carcinoma. For example, patients infected with HCV genotypes 1 or 4 tend to be more resistant to IFN-based therapies than genotypes 2 or 3 [11]. Genetic variation within the core, E2, NS2, P7, NS5A, and NS5B proteins appears to be

related to IFN resistance [12] by interfering with IFN pathways and antiproliferative activity and contributing to carcinogenesis [13].

Host Interferon Response to HCV Infection

HCV does not kill the cells it infects, but triggers an immune-mediated inflammatory response (hepatitis) that either rapidly clears the infection or slowly destroys the liver, resulting in the development of cirrhosis and liver cancer. The outcome is largely determined by the efficiency of the antiviral immune response. [14]. The strong interferon response to HCV infection produces IFN-β secretion from the infected cell. IFN-β binding to the IFN-α/β receptor signals the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which leads to upregulation of several hundred interferon-stimulated genes (ISGs). ISG products impart viral regulatory functions that limit HCV replication by disrupting viral RNA translation and inhibiting antigenomic strand RNA synthesis. In addition to its direct antiviral actions, IFN primes the maturation of immune effector cells and potentiates the production of other pro-inflammatory cytokines by resident hepatic cells; this process indirectly modulates cell-mediated defenses and adaptive immunity to HCV [14]. Current IFN-based therapy exploits the mechanism of induction of ISG expression through the IFN-α/β receptor and JAK/STAT pathway to provide antiviral action against HCV [12].

Treatment

Chronic HCV infection imposes a major public health burden in part because therapy may not be effective and usually has major side effects. HCV elimination is operationally defined as causing a sustained virological response (SVR) in which HCV RNA levels cannot be detected in blood 6 months after cessation of therapy [15]. A combination therapy with peg-interferon alpha (peg-IFN) and ribavirin (RBV) is effective in eliminating HCV in only about half of patients treated [16]. Success rates are even lower in certain subpopulations, such as African Americans, who have an almost 50% reduction in SVR rates with pegIFN and RBV compared with Caucasians [17]. Another class of drugs recently approved for use by the FDA – direct-acting antiviral agents (DAA), such as telaprevir or boceprevir – cause antiviral resistance and virological breakthrough when used as solo therapy. However, triple-regimen therapy with a DAA plus peg-IFN and RBV greatly enhances SVR rates, up to 75% in patients with genotype 1 chronic HCV infection, the most prevalent genotype in the US; DAAs are not yet widely available or are too costly in most of the world [15, 18–20].

Because IFN is the backbone of all therapeutic regimens, identifying factors that affect the response to IFN therapy is important for clinical decision-making. Several pre- and on-treatment host and viral variables have been associated with treatment outcome, and some of these have become part of decision-making for treatment [21]. Young age, female gender, lower weight, normal serum glucose, absence of hepatic steatosis, no or minimal fibrosis on liver biopsy, adherence to therapy, lower baseline viral load, and genotypes 2 and 4 are positive predictors of SVR [17]. One of the most important predictors of SVR when using a combination therapy of pegIFN and RBV is the specific host *IL28B* genotype [22].

Host *IL28B* Genotype, Ethnicity and Response to Interferon Treatment

In late 2009 and early 2010, the association between the *IL28B* genotype and treatment outcome in HCV genotype 1 infection was made by 4 independent groups in genome-wide association studies [23–26]. All found that single nucleotide polymorphisms (SNPs) rs12979860 and rs8099917 – which tag a haplotype block on chromosome 19 that spans *IL28B* – strongly predict the outcome of pegIFN and RBV treatment in patients infected with HCV genotype 1. This finding was consistent among different racial and ethnic populations (African American, Asian, Caucasian, and Hispanic). The SNP most associated with SVR in Caucasians is rs12979860, whereas in Asians it seems to be rs8099917. Individuals carrying the favorable response genotype, containing either rs12979860-CC or rs8099917-TT, are at least twice as likely to attain SVR [27–30]. In most populations, except African Americans, these 2 SNPs are in strong linkage disequilibrium and similarly informative.

The frequency of the favorable response genotype differs across racial/ethnic populations, being most frequent in Asians (73%), least frequent in African Americans (13%) and with an intermediate frequency in Caucasians (41%) and Hispanics (25%) [23–26, 28, 30]. Although the favorable response genotype has a similar effect on treatment response in all racial/ethnic groups (Caucasians, odds ratio (OR) = 3.88, (95% CI) = (2.75–5.49); African American, OR = 4.63 (2.52–8.50); Asians, OR = 5.66 (3.99–8.02); pooled OR = 4.68 (3.75–5.83)), its differential distribution contributes very strongly to observed racial disparities in overall treatment response [28]. Indeed, African American patients with a favorable genotype respond better than Caucasian patients with an unfavorable genotype [23]. However, the *IL28B* genotype does not account for all of the racial differences in response to treatment; both *IL28B* genotype and ethnic background independently predict SVR [31].

Several studies have found that *IL28B* variants are also associated with likelihood of spontaneous clearance of HCV infection. [25, 32–34]. Patients who carry the favorable response genotype are twice as likely to clear acute HCV infection without treatment (rs12979860-CC, OR = 3.75 (2.42–5.81); rs8099917-TT, OR = 2.67 (1.82–3.91)) [34]. The relationship of *IL28B* genotype with pegIFN and RBV treatment outcome is similar in patients infected with only HCV and those coinfected with HCV and HIV [30, 35]. However, *IL28B* genotype has no effect on outcomes of HIV or HBV infection or elite control of HIV infection [36–38].

The consistently replicated association of genetic variants of *IL28B* with treatment outcome suggests that its product, interferon lambda 3 (IFN-λ3), has an important role in determining viral clearance [39]. The 3 IFN-λs coded by *IL28A, IL28B* and *IL29* were originally discovered in 2003 through computational prediction of previously unknown proteins from genomic sequence data. The signaling and biological activities of these 3 IFN-λs overlap with IFN-α, signaling via the same JAK/STAT pathway leading to induction of IGS expression and antiviral proteins. IFN-λ1/2 have shown antiviral activity against HCV in vitro, although they are less potent than IFN-α. In a phase 1 study of patients with genotype 1 chronic HCV infection, pegIFN-λ1 had potent antiviral activity and resulted in a better side-effect profile than IFN-α [40]. These outcomes might be due to the fact that the

common receptor (IFN-λR) shared by IFN-λs has a more liver-specific distribution than IFN-αR. It seems highly likely that the IFN-λ axis will lead to viable therapeutic options in the near future.

IL28B variants are the strongest baseline predictor of SVR to pegIFN plus RBV in treatment-naïve patients with genotype 1 HCV in multivariable models with other independent predictors such as race, baseline viral load, hepatic fibrosis stage, and fasting glucose level, across different racial and ethnic populations (African American, Asian, Caucasian, and Hispanic) [23, 41, 42]. Patients infected with HCV genotype 1 who have a favorable *IL28B* genotype have a 65% chance of cure with pegIFN and RBV. The favorable *IL28B* response genotype is associated with more rapid viral kinetics and improved the treatment outcome independent of ISG expression [41].

IL28B Genotype in the Era of DAAs

The treatment regimen for chronic HCV is currently undergoing a major change with the introduction of DAAs. DAAs directly inhibit specific steps in the HCV viral life cycle, for example, currently approved boceprevir and telaprevir target NS3 protease. Boceprevir or telaprevir in combination with pegIFN and RBV are now considered as optimal therapy for chronic HCV genotype 1 infection; both therapies must be given with pegIFN and RBV to limit selection of resistant variants and improve antiviral response [15, 22, 43]. Triple therapy with boceprevir or telaprevir improves on-treatment kinetics and increases achieved SVR rates.

Initial data suggest that *IL28B* genotype also predicts the response to DAA therapy, although its predictive effect might not be as strong as for dual therapy with pegIFN and RBV [44]. Patients with favorable *IL28B* genotype achieve 70% SVR with standard therapy and up to 90% achieve SVR with triple therapy. The major benefit of DAA appears to be to allow short treatment duration [45]. Patients with an unfavorable *IL28B* genotype have the most to gain from the addition of DAA, which doubles the SVR rate in this group (30% with pegIFN and RBV only, and 70% with triple therapy); for these patients, the cost-effectiveness and risk-benefit will be more favorable [45].

Public Health Implications

Currently, an estimated 3.2 million Americans are living with hepatitis C in the US, most of whom (2.1 million) were born from 1945 through 1965 (the 'baby boomers'). However, up to 1.5 million baby boomers have not sought medical treatment because they do not know they are infected. To limit HCV-associated morbidity and mortality, the Centers for Disease Control and Prevention recently recommended a one-time hepatitis C test for adults born during 1945–1964 to identify infected persons and link them to care and treatment [46, 47]. This recommendation follows an action plan for prevention, care, and treatment of viral hepatitis issued by the US Department of Health and Human Services in 2011 [48]. Implementation of this approach could identify 800,000 additional HCV infections and prevent more than 120,000 deaths by providing these patients with appropriate treatment [46, 47]. *IL28B* genotype testing could be part of a cost-effective strategy that also improves

individual outcomes [49]; a commercial test for *IL28B* is now available for about USD 300, needed to be performed only once in a patient's life [31].

DAA causes more severe adverse effects than pegIFN and RBV alone [50]; because it is costly (USD 1,100 per week for boceprevir, USD 4,100 per week for telaprevir and USD 954 per week for pegIFN and RBV), access to DAA could be restricted. Universal triple therapy with boceprevir (USD 1,100 per week) in all HCV genotype 1 infected patients in the US would cost an additional USD 102,600 per quality adjusted life year (QALY) gained in the setting of mild fibrosis, compared with the standard dual therapy with pegIFN and RBV. Using IL28B guided triple therapy could improve cost-effectiveness; for example, treating only those patients with unfavorable *IL28B* genotypes with a protease inhibitor would cost USD 70,100 per QALY in those with mild fibrosis or USD 36,300 per QALY with advanced fibrosis in addition to therapy with pegIFN and RBV therapy alone [49]. *IL28B* genotype identifies patients who are likely to attain SVR with a shorter, lower-cost regimen (pegIFN and RBV alone); therefore, genetic testing could be helpful in maximizing the cost-effectiveness of triple therapy. For example, offering patients with favorable *IL28B* genotypes first-line treatment with pegIFN and RBV, followed by DAA for those who relapse, could be more cost-effective than treating all patients initially with regimens including DAA [45, 49].

As there is substantial overlap between persons infected with HCV and HIV, coinfected individuals represent an important subgroup with chronic HCV infection being one of the leading causes of morbidity and mortality among persons with HIV infection [51]. Despite the introduction of promising therapies and the ability to assess therapy response through *IL28B* testing, treatment up-take for HCV is unacceptably low, especially among substance abusers. Increasing the awareness of these diagnostic and treatment advances among health care providers may help to improve treatment uptake among all individuals with chronic HCV infection [51].

Conclusion

IL28B variation is strongly associated with response to pegIFN plus RBV therapy in patients chronically infected with HCV genotype 1. This discovery has been consistently replicated in many populations. *IL28B* genotype is a strong predictor of treatment outcome at the individual level. Even with the introduction of a new class of highly effective DAAs, the *IL28B* genotype continues to serve as a useful predictor of treatment outcome and could help to establish treatment expectations and guide decisions for retreatment of prior nonresponders as long as IFN continues to be the backbone for antiviral therapy. Testing for *IL28B* variants predictive of therapeutic success should contribute substantially to clinical decision-making and formulation of public health policies. The goal of personalized healthcare may be one step closer for patients with HCV infection.

Acknowledgement

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