REVIEW

Pharmacogenetics of hepatitis C: transition from interferon-based therapies to direct-acting antiviral agents

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Abstract: Hepatitis C virus (HCV) has emerged as a major viral pandemic over the past two decades, infecting 170 million individuals, which equates to approximately 3% of the world's population. The prevalence of HCV varies according to geographic region, being highest in developing countries such as Egypt. HCV has a high tendency to induce chronic progressive liver damage in the form of hepatic fibrosis, cirrhosis, or liver cancer. To date, there is no vaccine against HCV infection. Combination therapy comprising PEGylated interferon-alpha and ribavirin has been the standard of care for patients with chronic hepatitis C for more than a decade. However, many patients still do not respond to therapy or develop adverse events. Recently, direct antiviral agents such as protease inhibitors, polymerase inhibitors, or NS5A inhibitors have been used to augment PEGylated interferon and ribavirin, resulting in better efficacy, better tolerance, and a shorter treatment duration. However, most clinical trials have focused on assessing the efficacy and safety of direct antiviral agents in patients with genotype 1, and the response of other HCV genotypes has not been elucidated. Moreover, the prohibitive costs of such triple therapies will limit their use in patients in developing countries where most of the HCV infection exists. Understanding the host and viral factors associated with viral clearance is necessary for individualizing therapy to maximize sustained virologic response rates, prevent progression to liver disease, and increase the overall benefits of therapy with respect to its costs. Genome wide studies have shown significant associations between a set of polymorphisms in the region of the *interleukin-28B* (*IL28B*) gene and natural clearance of HCV infection or after PEGylated interferon-alpha and ribavirin treatment with and without direct antiviral agents. This paper synthesizes the recent advances in the pharmacogenetics of HCV infection in the era of triple therapies.

Keywords: hepatitis C virus, interleukin-28B polymorphisms, PEGylated interferon and ribavirin, direct-acting antiviral agents, pharmacogenetics, rational therapeutics

Introduction

The World Health Organization estimates that 170–200 million people worldwide, ie, 3% of the world's population, is infected with hepatitis C virus (HCV).[1] In the USA, nearly 2% of the population is infected.[2] In northern parts of Europe, the prevalence is less than 0.1%, but increases to more than 1% in the south.[3] The prevalence of HCV infection is greater in Africa and Asia, with infection rates exceeding 5%.[1,4] Egypt has the highest prevalence of hepatitis C in the world, with 15% of the population affected.[5,6]

Acute HCV infection is mostly asymptomatic and rarely recognized clinically. Spontaneous viral clearance (SVC) occurs in approximately 25% of patients.[7] The striking feature of HCV infection is its tendency to persist and develop

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into chronic hepatitis. Some patients with chronic HCV are at increased risk of developing liver cirrhosis and hepatocellular carcinoma and will eventually develop serious sequelae.[8,9]

The treatment available for HCV has changed significantly over recent decades, with the standard of care shifting from conventional interferon (IFN) monotherapy to IFN and ribavirin combination therapy to PEGylated IFN (PEG-IFN) with ribavirin. IFNα has potent antiviral activity due to its ability to induce IFN-stimulated genes that encode proteins which inhibit various stages of viral replication.[10] In addition, IFNα has an immunomodulatory effect, interacting with both the adaptive and innate immune response of the host. IFNα promotes T-helper (Th) cell differentiation of T-lymphocytes over Th2 cells, leading to increased production of interleukin (IL)-2 and IFNγ. In addition, IFNα exerts an anti-inflammatory effect by inhibiting the synthesis of various cytokines, including tumor necrosis factor-alpha and IL-1.[11] IFNα binds with its specific receptor on the surface of target cells, activating an intracellular signaling cascade, which causes the induction of IFN-stimulated genes (ISGs), establishing a nonvirus-specific antiviral state inside the cell.[12,13] Janus kinase/signal transducers and activators of transcription pathway are the principal signaling mechanisms used by IFNα.[14]

Cytoplasmic proteins with the activity of tyrosine kinase associated with IFNα receptor, activated Jak1, and tyrosine kinase 2 are activated by dimerization of the receptors. Activated Jak1 and tyrosine kinase 2 phosphorylate STAT1 and STAT2, respectively. Phosphorylated STAT1 and STAT2 bond with protein p48, forming IFN-stimulated gene factor 3, that translocates into the nucleus and binds with IFN-stimulated regulatory element in the sequences that promote a variety of genes inducible by IFNα, including antiviral proteins such as 2′5′-oligoadenylate synthetase, protein kinase RNA, and Mx protein.[12–15]

The mechanisms of action of ribavirin are not fully understood. It has been postulated that ribavirin acts via direct inhibition of HCV replication, inhibition of the host inosine monophosphate dehydrogenase enzyme, induction of mutagenesis to drive a rapidly replicating virus beyond the threshold to error catastrophe, and immunomodulation by inducing a Th1 immune response.[16]

The percentages of patients achieving a sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks after completion of treatment, improved significantly with advances in the therapeutic regimens available. However, SVR rates are still below target,

especially for the difficult to treat HCV genotypes 1 and 4. Management of relapsers and nonresponders remains a challenging and controversial issue. In addition, all of the aforementioned IFN-based regimens have moderate to severe side effects, including hematologic adverse events (neutropenia, thrombocytopenia), fatigue, irritability, fever, myalgia, arthralgia, inflammation at the injection site, and cardiac dysrhythmia, that negatively influence the tolerability and adherence of patients with therapy. The prohibitive cost of treatment is another problem facing patients in developing countries where most cases of chronic HCV are clustered.

All of the above factors have driven a need to develop new treatments that are safer and more effective. Recently, a number of direct-acting antiviral agents (DAAs) have been developed for use with PEG-IFN/ribavirin as triple therapies or IFN-free therapy. The efficacy of such therapies varies according to genotype and host characteristics. This paper provides an overview of advances made in understanding the pharmacogenetics of HCV infection during the transition from IFN-based therapies to triple therapies and IFN-free regimens.

Acute hepatitis C: an emerging field of pharmacogenetics

The percentage of patients with clinically diagnosed acute HCV infection is low, since 70%–80% of acute HCV infections are asymptomatic.[7–10] To date, there are no reliable criteria to predict patients in whom HCV infection will spontaneously resolve and those who will develop chronic infection. The acute phase of the infection is the period during which PEG-IFNα monotherapy is associated with high response rates of up to 80%–90%.[17–24] It is generally acceptable to treat patients with acute HCV who fail to clear viremia 3 months after infection with 12–24-week courses of PEG-IFNα monotherapy.[17–19] SVR rates decrease markedly when treatment is not started until the chronic phase of infection.[19] Being able to predict which patients with acute HCV infection are likely not to clear HCV spontaneously is critical for the success of acute HCV therapy, because it will enable physicians to initiate therapy early to eradicate HCV, prevent chronic evolution of the disease, and avoid the adverse events of long-term combination PEG-IFN and ribavirin therapy. Thus, an indepth understanding of the molecular mechanisms and genetic determinants of spontaneous resolution will help to identify reliable biomarkers for acute HCV clearance and determine new targets to personalize treatment strategies for acute HCV infection.

Determinants of spontaneous resolution of acute HCV

Some clinical features have been associated with SVC in patients with acute HCV. Patients younger than 40 years of age, children, women, and patients with symptomatic disease, particularly jaundice, are more likely to undergo spontaneous resolution.[10,17,24–28]

Viral factors

Some virologic factors have been associated with spontaneous resolution. Farci et al[29] showed that acute resolving hepatitis was associated with HCV homogeneity, whereas progressing hepatitis was associated with genetic diversity, presumably reflecting greater immune pressure during acute spontaneous clearance. Individuals coinfected with HCV and human immunodeficiency virus (HIV)[30,31] or with HCV and *Schistosoma mansoni* are far less likely to clear HCV spontaneously.[32–35] Additionally, patients with compromised immune systems, such as organ transplant recipients, frequently progress to chronic infection.[36]

Immunologic factors

Early events in the interaction between HCV and the immune system likely determine the outcome of infection. Clearance of HCV is associated with the development of robust and multispecific CD4+ and CD8+ T-cell responses in the blood and liver that can persist for years after recovery from the acute disease.[29] In contrast, individuals who progress to chronic infection fail to mount such a response or may have inadequate production of the cytokines essential for control of viral replication. Incomplete control of viral replication by CD8+ T-cells in the absence of sufficient memory CD4+ T-cells leads to viral persistence and emergence of cytotoxic T-lymphocyte escape mutants.[37–40] However, it is still not clear why so few individuals mount a successful HCV-specific immune response capable of eradicating the infection and the majority fail to do so.

Genetic factors

Genetic studies have shown that individual genetic make-up is an important host determinant for outcome and progression of acute HCV infection. One study showed that genes encoding the inhibitory natural killer cell receptor KIR2DL3 and its human leukocyte antigen C group 1 (*HLA-C1*) ligand influenced the likelihood of spontaneous resolution of HCV infection, suggesting that inhibitory natural killer cell interactions are critical for antiviral immunity.[41] IL-18 is a pivotal mediator of the Th1/Th2-driven immune response.

IL-18 promoter polymorphisms (−607C/A and −137G/C) were found to be associated with SVC.[42]

IL28B polymorphism and outcome of acute HCV

Genome wide association studies have added new insights into the pathophysiology and pharmacology of HCV infection. Genome wide association studies have the advantage of focusing resources on a manageable number of genes and polymorphisms that are likely to be important. The strength of genome-wide screening is its ability to reveal not only genes expected to play a significant role, but also genes that are not involved in the pathogenesis of the disease. Polymorphisms of genes involved in innate immunity as well as those of genes encoding cytokines and other immunologic mediators may explain spontaneous recovery from acute HCV and influence the strength and nature of immune defense.

IL28B is located on chromosome 19 and encodes IFN-lambda (IFNλ), a newly described family of type III IFN that is distantly related to type I IFNs and IL-10. IFNλ includes IFNλ 1, 2 and 3, also known as IL29, IL28A, and IL28B.[43] Several studies[24,44–48] have shown that single nucleotide polymorphisms (SNPs) in the *IL28B* region may play a critical role in determining the outcome of acute infection (clearance versus persistence). A strong association has been found between polymorphisms in or near *IL28B*, the pathogenesis of HCV, and outcome of acute HCV infection. Ge et al[47] observed that the C allele occurred more frequently in patients with spontaneous clearance. Further, Thomas et al[44] showed that the SNP rs12979860 upstream of *IL28B* and the C/C genotype were associated with spontaneous clearance of HCV, and this finding was confirmed by recent studies in patients with acute HCV.[37,41] Interestingly, jaundice during acute infection was more common in patients with the C/C genotype.[24,46] The T/T genotype occurred more often in people of African descent, had an intermediate frequency among Europeans, and a lower frequency among Asians, a finding that partly explains the ethnic differences seen in spontaneous acute HCV recovery rates across different ethnic groups. The risk variant of the *IL28B* gene may produce IFNλ that may affect the adaptive immune response and IFN-stimulated genes.[44]

In a recent study[24] of a well characterized cohort of acute HCV patients, we showed that a decrease in alanine aminotransferase within 4 weeks (odds ratio [OR] 6.83; $P<0.0001$), jaundice (OR 3.54; $P=0.001$), female sex (OR 2.39; $P=0.007$), and a $>2.5 \log_{10}$ decrease in HCV-RNA

within 8 weeks (OR 2.48; *P*=0.016) were independently associated with spontaneous clearance. *IL28B* CC was also associated with a multispecific T-cell response (r^2=0.0.835; $P<0.001$). These findings have important implications for predicting the outcome of HCV exposure and acute infection and identifying patients likely to benefit from therapy.

Taken together, genetic variations play an important role in spontaneous resolution or persistence of HCV infection. Given the benefits of early treatment of acute HCV and the critical timing of initiation of therapy,[11–16,25] integrating genetic markers such as *IL28B* genotyping into the matrix of diagnostics for acute HCV will help to target therapy to individuals with a high likelihood of developing chronic HCV infection and eradicate the virus with a short regimen of PEG-IFNα monotherapy.

Chronic HCV therapy: from IFN-based therapies to direct-acting antiviral agents

Despite extensive efforts, there is still no vaccine available for HCV. Thus, control of HCV infection depends on preventive measures, early detection, and treatment of acute or chronic infection.

PEG-IFN and ribavirin therapy

The current standard of care is PEG-IFNα-2b and ribavirin-based therapy. The primary goal of antiviral therapy in patients with chronic hepatitis C is achieving an SVR, defined as undetectable serum HCV-RNA by a sensitive molecular assay 24 weeks after completion of therapy. Although the standard of care improves SVR rates in HCV genotypes 2 and 3, the response is still suboptimal in genotypes 1 and 4 and in particular patient populations. Furthermore, antiviral therapy is associated with several adverse events and high costs that represent a huge burden for developing countries. Thus, individualization and personalization of treatment with identification of factors associated with SVR are critical to maximize efficacy and spare patients preventable adverse events and expense. A number of host and viral factors influence SVR rates in patients with chronic HCV. An SVR is more likely in young individuals, females, patients infected with genotypes 2 or 3, and those with low pretreatment HCV-RNA levels, no or minimal liver fibrosis, and adequate adherence to therapy.[49–60] Infection with HCV genotype 1 or 4, high baseline HCV RNA levels (>800,000 IU/mL), steatosis, insulin resistance, and coinfection with HIV are associated with low response rates.[49–52]

In an effort to improve rates of sustained response to therapy in patients with chronic HCV infection, various strategies have been adopted to tailor the treatment duration according to the on-treatment response. A number of studies have investigated shortened courses of treatment to minimize adverse effects and costs without compromising efficacy. In patients with chronic HCV genotype 2 or 3 who had undetectable HCV-RNA at 4 weeks of therapy (rapid virologic response), a shorter PEG-IFNα and ribavirin regimen (12–24 weeks) was associated with SVR rates similar to those achieved with 48 weeks of treatment.[53,54] Clinical trials have also demonstrated the efficacy of 24 weeks of combination PEG-IFN and ribavirin therapy in patients with chronic hepatitis genotype 1 and 4, who achieved a rapid virologic response defined as undetectable viremia after 4 weeks of treatment.[50,51,58–60]

Direct-acting antiviral agents

DAAs were developed to improve SVR rates, reduce adverse events, and improve adherence to therapy in HCV patients. These drugs target the different stages of virus development and replication. Production of DAAs was heralded by extensive research to clarify the viral life cycle of HCV in an attempt to develop novel drugs that terminate the cycle before its completion, thereby inhibiting development and replication of the virus. Several clinical trials investigating DAAs have yielded encouraging results that provide hope for patients with chronic HCV. DAAs can be classified into two main groups, ie, first-generation and second-generation protease inhibitors.

First-generation protease inhibitors

The most important DAAs belong to the class of protease inhibitors targeting NS3/4 protease. These first-generation protease inhibitors have been assessed in large clinical trials. Boceprevir and telaprevir are the first-generation oral protease inhibitors. These agents have been approved by regulatory authorities and are currently used in clinical practice. Boceprevir acts as a noncovalent inhibitor of cytochrome P450 A4 and P-glycoprotein. Addition of boceprevir or telaprevir to PEG-IFN and ribavirin significantly increased SVR rates and shortened the treatment duration in naïve, relapsing, and partially responding patients.[61,62] The PEG-IFN/ribavirin/telaprevir regimen was associated with an SVR of 75% in patients who received the combination for 12 weeks.[61] The SPRINT-2 trial (ClinicalTrials.gov registry number NCT00705432), which included more than 1,000 previously untreated adults with HCV genotype 1 infection,

reported SVR rates of 63% in the response-guided boceprevir group and 66% in the fixed-duration boceprevir group, compared with 38% in the PEG-IFN/ribavirin group.[62]

Consequently, current practice guidelines recommend a triple therapy regimen combining PEG-IFN, ribavirin, and telaprevir or boceprevir. In the case of telaprevir, triple therapy is administered for the first 12 weeks followed by a period of dual PEG-IFN/ribavirin therapy for a total of 24–48 weeks, depending on response. In the case of boceprevir, dual PEG-IFN/ribavirin therapy is given for the first 4 weeks followed by a period of 44 weeks of triple therapy.[63] However, triple therapy with boceprevir or telaprevir has some drawbacks, including drug–drug interactions and viral resistance.

Although triple therapy has improved SVR rates, this regimen increases adverse events such as rash and moderate to severe anemia to an extent that might require reduction of the ribavirin dose. Patient adherence to and tolerability of triple therapy including boceprevir or telaprevir is a challenging issue because these two DAAs should be given three times daily with food. Boceprevir and telaprevir are only effective against genotype 1, with recent studies showing that these protease inhibitors have no antiviral activity against genotype 2, 3, or 4. Further, triple therapy is ineffective in patients who have not responded to previous dual PEG-IFN/ribavirin therapy. From an economic perspective, triple therapy has dramatically increased the costs of HCV treatment, which are originally prohibitive.

Second-generation protease inhibitors

Second-generation protease inhibitors, such as simeprevir, asunaprevir, and danoprevir, are currently being evaluated in an effort to overcome the limited efficacy of the first-generation protease inhibitors in HCV genotypes 2, 3, and 4 and to minimize their adverse events.[64]

The PILLAR (PIvotaL Lymphoma triAls of RAD001) trial[65] investigated the efficacy and safety of two different simeprevir doses administered once daily with PEG-IFNα-2a and ribavirin in treatment-naïve patients with HCV genotype 1 infection. According to response-guided therapy criteria, 79.2%–86.1% of simeprevir-treated patients completed treatment by week 24; 85.2%–95.6% of these patients subsequently achieved an SVR. The safety profile of triple therapy including simeprevir was found to be comparable with that of combination PEG-IFN/ribavirin therapy.

Triple therapy comprising danoprevir, PEG-IFNα-2a, and ribavirin was assessed in a clinical trial conducted in patients with chronic HCV genotype 1. SVR rates were higher in patients given danoprevir 300 mg (68%), 600 mg

(85%), and 900 mg (76%) than in those on placebo (42%). Seventy-nine percent of patients given danoprevir 600 mg had a rapid virologic response; among these, 96% had an SVR. Serious adverse events were reported in 7%–8% of patients given danoprevir and four patients given danoprevir (one patient in the 600 mg group and three in the 900 mg group) had reversible grade 4 increases in alanine aminotransferase, which led to early discontinuation of the 900 mg arm of the study.[66]

In the DAUPHINE trial (ClinicalTrials.gov registry number NCT0122094), treatment-naïve patients with HCV genotype 1 or 4 were randomized to receive twice-daily danoprevir/ribavirin 200/100 mg, 100/100 mg, or 50/100 mg plus PEG-IFN and ribavirin for 24 weeks; twice-daily danoprevir/ribavirin 100/100 mg plus PEG-IFN and ribavirin for 12 or 24 weeks; or PEG-IFN and ribavirin alone for 48 weeks. Patients in the response-guided therapy arm with an extended rapid virologic response (HCV RNA <15 IU/mL during weeks 2–10) stopped all therapy at week 12; patients without an extended rapid virologic response continued all treatment to week 24. The combination of danoprevir/ribavirin plus PEG-IFN and ribavirin was an effective and safe therapy in treatment-naïve patients with HCV genotype 1 or 4 infection.[67]

Polymerase inhibitors

Polymerase inhibitors are another class of DAAs that have recently shown much potential. These drugs bind to NS5B polymerase to halt replication of the virus. Nucleoside analog inhibitors, a category of polymerase inhibitors, are incorporated into the HCV RNA chain leading to direct chain termination. They are potentially active against all HCV genotypes, and viral resistance to these agents is low and less frequent than with non-nucleoside inhibitors, the other class of polymerase inhibitors that bind to several discrete sites outside of the polymerase active center, causing a conformational protein change.[68]

Sofosbuvir is a nucleoside analog inhibitor and has recently been approved by the US Food and Drug Administration. It has a high barrier to viral resistance, and no virologic breakthrough has been recorded so far. One major feature of sofosbuvir is its pan-genotypic antiviral effect. It is given orally once a day and does not require concurrent or prior food intake.[68] Several treatment strategies involving sofosbuvir have been considered and tested.[69,70] The first strategy is to add sofosbuvir to PEG-IFN and ribavirin. One study[69] has assessed the safety and efficacy of sofosbuvir in combination with PEG-IFN and ribavirin in 316 noncirrhotic

treatment-naïve patients with HCV genotype-1 (52 to cohort A, 109 to cohort B, 155 to cohort C, and eleven with HCV genotype 4 and five with genotype 6 to cohort D). In patients with HCV genotype 1, SVR24 was achieved by 46 patients (89%, 95% confidence interval [CI] 77–96) in cohort A, 97 patients (89%, CI 82–94) in cohort B, and 135 (87%, CI 81–92) in cohort C. There was no difference in the proportion of patients achieving SVR24 in cohort A and cohort B (P=0.94) or cohort C (P=0.78). Nine (82%) of the eleven patients with genotype 4 and all five with genotype 6 achieved SVR24.

Interferon-free sofosbuvir regimen

Another strategy is to use sofosbuvir and ribavirin without PEG-IFN. Gane et al[71] evaluated an all-oral regimen comprising the nucleotide polymerase inhibitor sofosbuvir with the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 in 113 patients with genotype 1 HCV infection. Sofosbuvir (400 mg once daily) and ledipasvir (90 mg once daily) plus ribavirin were given for 12 weeks to treatment-naïve patients (n=25) and those who did not respond to previous therapy (prior null responders, n=9). Sofosbuvir and GS-9669 (500 mg once daily) plus ribavirin were given for 12 weeks to treatment-naïve patients (n=25) and prior null responders (n=10). Additionally, prior null responders with cirrhosis were randomly assigned to receive a fixed-dose combination of sofosbuvir and ledipasvir, with ribavirin (n=9) or without ribavirin (n=10). Finally, a group of treatment-naïve patients received sofosbuvir, ledipasvir, and ribavirin for 6 weeks (n=25). SVR12 was achieved by 25/25 (100%) treatment-naïve patients receiving sofosbuvir, ledipasvir, and ribavirin and 23/25 (92%) of those receiving sofosbuvir, GS-9669, and ribavirin. Of the 25 treatment-naïve patients receiving 6 weeks of sofosbuvir, ledipasvir, and ribavirin, 17 (68%) achieved SVR12. All noncirrhotic prior null responders receiving 12 weeks of sofosbuvir along with another direct-acting antiviral agent plus ribavirin achieved an SVR12, ie, 9/9 (100%) of those receiving sofosbuvir, ledipasvir, and ribavirin and 10/10 (100%) of those receiving sofosbuvir, GS-9669, and ribavirin. Among cirrhotic prior null responders, SVR12 was achieved by nine (100%) of those receiving sofosbuvir, ledipasvir, and ribavirin, and seven (70%) of those receiving sofosbuvir and ledipasvir without ribavirin.[71]

An open-label study[72] randomized 100 noncirrhotic treatment-naïve patients to receive sofosbuvir plus ledipasvir for 8 weeks (group 1), sofosbuvir plus ledipasvir and ribavirin for 8 weeks (group 2), or sofosbuvir plus ledipasvir for 12 weeks (group 3). This trial showed that the fixed-dose sofosbuvir-ledipasvir combination alone or with ribavirin has the potential to cure most patients with HCV genotype 1, irrespective of treatment history or the presence of compensated cirrhosis.

Pharmacogenomics for individualization of HCV therapies

Pharmacogenomics could play a crucial role in optimizing HCV therapy by taking into account ethnic variations in response to therapy,[73] identifying variations in treatment response, elucidating the molecular mechanisms of current and future therapies, and development of innovative genetic tools that will enable physicians to individualize drug therapy, adjust dosages, and reduce the likelihood of adverse effects and therapeutic costs.

IL28B polymorphism and outcome of chronic HCV therapy

The link between *IL28B* and the outcome of HCV reported by several groups has revolutionized our understanding of host determinants of treatment response. Several independent studies[74–94] have demonstrated a strong association between polymorphisms in or near the *IL28B* and SVR to IFN-based therapy or triple PEG-IFN, ribavirin, and DAA therapies (Table 1). These findings have increased our understanding of the genetic basis of response to therapy.

Ge et al[47] demonstrated that patients with the C/C genotype have a greater likelihood of HCV clearance than those with the C/T and T/T genotypes. The C allele is more frequent in individuals of European ancestry than in those of African ancestry, suggesting that the prevalence of C/C may account for ethnic differences in HCV clearance rates.

Tanaka et al[74] and Suppiah et al[75] reported that several relevant *IL28B* polymorphisms on chromosome 19 were associated with the outcome of IFN therapy. In Japanese patients, polymorphism in the SNP rs8099917 was a better predictor of response to PEG-IFNα/ribavirin therapy than other SNPs associated with *IL28B*.[76] Darling et al[77] and Lagging et al[78] demonstrated that quantitation of pretreatment serum IFNγ-inducible protein-10 improves the predictive value of an *IL28B* gene polymorphism for response to HCV treatment.

Two studies[79,80] have investigated the intrahepatic expression of ISGs and genetic variation in *IL28B* (rs8099917) in Japanese and North American patients with chronic hepatitis C who received combination PEG-IFN and ribavirin therapy. Gene expression profiling of the liver showed that a high proportion of nonresponders had upregulated ISG. Expression of

Table 1 Genetic studies on the relationship between *IL28* polymorphism and the outcome of HCV infection and therapy

Study	Cohort	IL28B SNPs	Results
Impact of host genetics on spontaneous resolution of acute and recent HCV infection			
Kamal et al[24]	165 patients with recent exposure to HCV	rs12979860	*IL28B* CC genotype, multispecific HCV T-cell responses, rapid decline in ALT, and viral load predict spontaneous clearance and response to acute HCV therapy in genotype 4. *IL28B* CC genotype correlates with developing early multispecific T-cell responses
Tillman et al[48]	90 women from the German anti-D cohort infected with HCV genotype 1b	rs12979860	Association of rs12979860 with spontaneous clearance of HCV. Women with the C/T or T/T genotype who did not develop jaundice had a lower chance of spontaneous clearance of HCV infection
Grebely et al[46]	163 Australians	rs8099917	Spontaneous clearance in 23%. Among participants with *IL28B* genotyping, rs8099917 TT homozygosity (versus GT/GG) was the only factor independently predicting time to spontaneous clearance
Rauch et al[45]	347 Swiss patients with spontaneous HCV clearance	rs8099917	The rs8099917 minor allele was associated with progression to chronic HCV infection
Thomas et al[44]	388 individuals with spontaneous resolution of HCV/620 individuals with persistent HCV infection	rs12979860	Association of rs12979860 and spontaneous clearance of HCV viremia. The C/C genotype strongly enhanced resolution of HCV infection in individuals of European or African ancestry
Impact of pharmacogenetics on outcome of PEG-IFNα and ribavirin therapy: chronic HCV genotype 1			
Tanaka et al[74]	Japanese patients with chronic HCV	rs12980275, rs8099917, rs8105790, rs11881222, rs8103142, rs28416813, rs4803219, rs8099917 and rs7248668	Association of SNPs, rs8099917 and rs12980027 with response to PEG-IFNα and ribavirin therapy
Ge et al[47]	European Americans (n=1,186) African-Americans (n=299) Hispanics (n=130)	rs12979860	Genetic polymorphism near the *IL28B* gene is associated with response to treatment in patients with European or African-American ancestry
Suppiah et al[75]	293 Australians with genotype 1 chronic HCV Validation cohort of 555 individuals	rs8099917	*IL28B* rs8099917 contributes to viral resistance
Thompson et al[84]	Chronic HCV patients (1,171 Caucasians, 300 African Americans, 116 Hispanics)	rs12979860	*IL28B* type CC was associated with improved early viral kinetics, RVR, complete EVR, and SVR
McCarthy et al[85]	1,021 patients with chronic HCV; 178 Caucasians and 53 African Americans, HCV genotypes 1 (n=186) and 2/3 (n=45)	rs12979860	*IL28B* type CC was the strongest pretreatment predictor of SVR rs12979860 genotype CC was found in 40% of Caucasians; rs12979860 genotype CC predicted SVR in Caucasians independent of HCV genotype
Rauch et al[45]	1,015 Europeans with chronic hepatitis C	rs8099917	Association of rs8099917 with failure to respond to therapy, particularly in patients with HCV genotype 1 or 4
Hayes et al[86]	817 Japanese patients with chronic HCV infection	rs12979860, rs8099917	Association of *IL28B* rs12979860 genotype CC with SVR Association of rs12979860 CT/TT genotype with nonresponse
Stättermayer et al[87]	754 PEG/ribavirin-treated patients (male/female =484/270; Caucasians 98.8%; mean age 42.8 [95% CI 42.0–43.6] years; genotype 1, n=435; genotype 2, n=23; genotype 3, n=185; genotype 4, n=114)	rs12979860, rs8099917	Of the treated patients, 12.9% had the ss469415590 ΔG/ΔG genotype (IFNL4), 51.3% were heterozygous (TT/ΔG) and 35.8% had TT/TT. IFNL4 polymorphism was independently associated with SVR in genotypes 1 and 4 but not in genotype 3. IFNL4 correlated strongly with rs12979860, but only moderately with rs8099917

(Continued)

Table 1 (*Continued*)

Study	Cohort	IL28B SNPs	Results
Sarrazin et al[88]	Chronic HCV genotype 1 patients (n=378), chronic HCV genotype 2/3 (n=267), and healthy controls (n=200) were included	rs8099917, rs12980275, and rs12979860	rs12979860 genotype CC, younger age, and genotype 2 were significantly associated with SVR in HCV genotype 2/3-infected patients
Darling et al[77]	115 nonresponders and 157 sustained responders; African Americans and Caucasian Americans	IL28B genotyping and quantitation of IFNγ-inducible protein-10	When combining *IL28B* genotype with pretreatment serum IFNγ-inducible protein-10 measurement, the predictive value for discrimination between SVR and nonresponse was significantly improved, especially in non-CC genotypes
Urban et al[80]	61 North American patients with chronic HCV	rs12979860 and whole-genome RNA expression in liver biopsies	*IL28B*-type was associated with SVR. No association was observed between *IL28B*-type and levels of liver *IL28B* or *IL28A* messenger RNA expression. ISG expression was associated with SVR
Impact of pharmacogenetics on outcome of chronic HCV non-1 genotype therapy			
Mangia et al[81]	268 chronic HCV Europeans: 213 infected with HCV genotype 2 and 55 infected with genotype 3	rs12979860	Association of CC genotype with SVR. Multivariable logistic regression model, *IL28B* genotype predicted SVR
Montes-Cano et al[90]	731 Spanish individuals: 284 were subjects with persistent infection, 69 with spontaneous resolution, 378 noninfected subjects	rs12979860	CC genotype was overrepresented among patients infected with viral genotypes non-1. An association was demonstrated between the CC genotype and SVR
Kawaoka et al[91]	719 Japanese patients with either HCV genotype 2a (n=530) or 2b (n=189)	rs8099917	Initial viral load and rs8099917 genotype are significant independent predictors of SVR in genotype 2 patients
Scherzer et al[92]	71 Caucasians with chronic HCV genotype 3	rs12979860, rs8099917	43 patients had RVR (C/C, 77.8%; C/T or T/T, 50.0%); irrespective of ribavirin dose, the viral load decline was larger than in patients with the T allele. In contrast with HCV genotype 1 patients, no effect on SVR rates was observed in genotype 3 patients
Stättermayer et al[87]	208 Caucasians with chronic HCV genotypes 2/3; 102 with HCV genotype 4	rs12979860, rs8099917	EVR was more likely among carriers of IL-28 polymorphisms rs12979860 C/C and rs8099917 T/T. RVR was more frequent in patients with the C/C allele. The positive predictive value of rs12979860 C/C for SVR was higher than that of rs8099917 T/T (80.5% versus 71.6%)
Impact of pharmacogenetics on outcome of PEG-IFNα + ribavirin + DAA therapy: chronic HCV genotype 1			
Poordad et al[62]	643 patients, naïve or previously treated. The DAA used was boceprevir	rs12979860	80.2% of patients with the CC genotype achieved SVR versus 65.7% of non-CC genotype patients. The CC polymorphism at *IL28B* rs12979860 was associated with a response to triple therapy and could identify candidates for shorter treatment durations. A ≥1 log(10) decrease in HCV RNA at week 4 of therapy was the strongest predictor of SVR, regardless of polymorphism in *IL28B*
Pol et al[94]	527 previously treated patients. The DAA used was TPV	rs12979860	79% SVR among the CC genotype patients, 60% SVR among CT genotype patients, and 61% SVR among TT genotype. *IL28B* genotype had a limited impact on SVR rates with TPV-based therapy in treatment-experienced patients. *IL28B* genotyping may have limited utility in the baseline evaluation of similar patients considered for TPV-based therapy
Furusyo et al[99]	120 Japanese patients. The DAA used was TPV	rs8099917	About 90% SVR in TT genotype patients, and 41.2%–68.4% SVR in non-TT genotype patients. TPV-based triple therapy can be successfully used to treat older patients with genotype 1b chronic hepatitis C

Study	Description	SNP	Results
Jacobson et al[61]	414 naïve patients. The DAA used was TPV	rs12979860	88.4% SVR among CC genotype patients and 65.8% SVR among non CC genotype patients
Akuta et al[97]	81 Japanese naïve and previously treated patients. The DAA used was TPV	rs8099917	Genetic variation near the IL28B gene and aa substitution of the core region are predictors of an SVR to triple therapy of TPV/PEG-IFN/ribavirin in Japanese patients infected with HCV genotype 1b
Lawitz et al[72]	327 naïve patients. The DAA used was sofosbuvir		A sustained virologic response occurred in 93 of 95 patients (98%) with the CC genotype of IL28B, as compared with 202 of 232 patients (87%) with the non–CC IL28B genotype
Chayama et al[95]	94 Japanese patients: 25 naïve, 44 relapsers, 25 nonresponders. The DAA used was TPV	rs8099917	Analysis of predictive factors identified IL28B SNP, rapid viral response, and transient response to previous therapy as significant independent predictors of SVR after triple therapy.
Bronowicki et al[96]	37 treatment-naïve patients from PROVE-2 (TPV)	rs12979860	94% SVR among TT genotype patients and 50% SVR among non-TT genotype patients
Zeusem et al[59]	Patients who did not respond (null response) had a partial response or relapsed after treatment with PEG-IFN and ribavirin received simeprevir (100 mg or 150 mg, once daily) for 12, 24, or 48 weeks plus PEG-IFN and ribavirin for 48 weeks (n=396), or placebo plus PEG-IFN and ribavirin for 48 weeks (n=66)	rs12979860	SVR: CC 94%, CT 67%, TT 33% / SVR (PEG-IFN/ribavirin arm): CC 64%, CT 31%, TT 25% (n=31)

Impact of IL28B on outcome of IFN-free regimen

Study	Description	SNP	Results
Marcellin et al[66]	83 chronic HCV patients assigned to mericitabine (500 or 1,000 mg twice daily) plus danoprevir (100 or 200 mg, every 8 hours, or 600 or 900 mg twice daily) or placebo	rs12979860	At day 14 (the end of IFN-free treatment), the mean reduction in serum HCV RNA level was slightly greater in patients with the CC polymorphism (5.01 $\log_{10}$ IU/mL) than in those without. Patients with CC also had a better on-treatment response, suggesting that the IL28B genotype has a positive influence on early viral kinetics in patients with chronic HCV receiving IFN-free treatment

Impact of pharmacogenetics on outcome of chronic HCV/HIV infection and therapy

Study	Description	SNP	Results
De Araujo et al[101]	26 HCV/HIV coinfected patients from South America, HCV genotypes 1 and 3	rs12979860	PEG-IFNα-2a was more effective in rs12979860 CC genotype carriers than in those with the TT/TC genotype. The first phase viral decline was greater in rs12979860 CC genotype than in TT/TC genotype. The second slower phase viral decline was greater in rs12979860 genotype CC than in genotype TT/TC in HCV genotype 1 patients
Rivero-Juarez et al[102]	260 Europeans patients coinfected with HIV/HCV genotype 1 and naïve to PEG-IFNα-2a and ribavirin (PEG-IFNα-2a/ribavirin)	rs12979860	No differences were found between HCV-1 subtypes in terms of HCV viral decline or rapid virological response rate. The effect of the IL28B CC genotype on HCV viral decline was observed only among patients infected with HCV-1b at all time points analyzed
Clausen et al[103]	206 Europeans with HIV and recent HCV infection	rs8103142, rs12979860, rs11881222	23% cleared HCV, 77% had chronic HCV IL28B polymorphism. HCV genotype and the host's genetic background affected the outcome of HCV infection. Association between IL28B SNP (rs8103142 CT, rs12979860 CT and rs11881222 AG) and decreased clearance rates of HCV

(Continued)

Table 1 (*Continued*)

Study	Cohort	IL28B SNPs	Results
Rallón et al[104]	650 Europeans (Spanish)	rs12979860	Association between rs12979860 and treatment outcome in HCV genotypes 1 and 4 patients coinfected with HIV
Aparicio et al[105]	160 Europeans coinfected with HIV and HCV genotype 1	rs8099917	rs8099917 G allele is highly prevalent in HCV/HIV patients. rs8099917 G allele is associated with treatment failure. rs8099917 genotyping is a good predictor of treatment outcome.
Medrano et al[106]	159 HIV-HCV coinfected Spanish patients	rs12979860	rs12979860 SNP, liver stiffness, genotype, and viral load are good predictors of SVR in HCV/HIV coinfected patients
Pineda et al[107]	154 HIV-HCV coinfected Spanish patients	rs12979860	IL28B polymorphisms are good predictors of SVR in HIV/HCV coinfected patients
Nattermann et al[108]	254 HIV-HCV coinfected Caucasians	rs12979860	In HIV patients with acute HCV, IL28B genotype was associated with serum levels of hepatitis C virus RNA, GGT, and CD4 cell count. In HIV patients with chronic HCV, the IL28B genotype was not associated with treatment response rates in patients with acute HCV infection
Impact of pharmacogenetics on outcome of antiviral therapy after liver transplantation			
Fukuhara et al[110]	67 Japanese liver recipients and 41 Japanese donors	rs8099917	IL28B mutations are predictors of SVR in the event of recurrent HCV infection after liver transplantation
Lange et al[111]	91 Europeans with liver graft reinfection (only 47 on treatment with PEG-IFNα and ribavirin)	rs12979860	Association between IL28B genetic background of the donor and treatment response in liver graft reinfection patients. The IL28B genetic background of the recipient does not greatly influence treatment response in liver graft reinfection patients. Association between donor IL28B rs12979860 CC and RVR, complete EVR, and SVR HCV RNA serum concentration and peak ALT in patients with donor IL28B rs12979860 CC is higher than patients with TT/CT genotype

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PEG-IFNα, PEGylated interferon alpha; DAAs, direct-acting antiviral agents; SVR, sustained virologic response; TPV, teleprevir; RVR, rapid virologic response; EVR, early virologic response; IL28B, interleukin-28B; IFN, interferon; SNP, single nucleotide polymorphism; ISG, interferon-stimulated gene; GGT, gammaglutamyl transferase.

hepatic ISG was strongly associated with treatment response and genetic variation of *IL28B*. Multivariate logistic regression analysis showed that ISG, fibrosis stage (F1 or F2), and mutation in the interferon sensitivity-determining region (≥ 2) were strongly associated with the viral response. Urban et al[80] found no association between *IL28B* type and levels of liver *IL28B* or *IL28A* messenger RNA expression.

IL28B polymorphisms and response of nongenotype 1 HCV infections to treatment

IL28B SNP rs12979860 was significantly associated with SVR to PEG-IFN/ribavirin therapy in chronic HCV genotype 2/3.[81] A study[82] has investigated the association of *IL28B* polymorphism with response to treatment or liver disease severity in a cohort of patients with HCV genotype 4. Carriers of the C/C allele of the *IL28B* gene SNP rs12979860 achieved significantly higher SVR rates (81.8%) when compared with 46.5% and 29.4% for genotypes CT and TT, respectively (*P*=0.0008). No significant relationship was found between rs12979860 and severity of disease. Another study[83] showed that the rs12979860, rs8099917, and rs11881222 *IL28B* SNPs were the strongest predictors of a response to PEG-IFN and ribavirin in patients with chronic HCV genotype 4.

Genetic polymorphism in *IL28B* and viral kinetics during therapy

Rapid and early virologic responses are important on-treatment predictors of response to PEG-IFN and ribavirin. Moreover, patients who achieve a rapid virologic response can be treated with 24 weeks rather than 48 weeks of standard therapy. In Caucasians, the CC *IL28B* type was associated with improved early viral kinetics and a greater likelihood of a rapid virologic response, complete early virologic response, and SVR compared with the CT and TT genotypes.[84] A similar relationship was seen in African Americans and Hispanics. In a multivariable regression model, the CC *IL28B* type was the strongest pretreatment predictor of SVR (odds ratio 5.2; 95% CI 4.1–6.7). However, rapid virologic response was a strong predictor of SVR regardless of *IL28B* type. An early virologic response to PEG-IFN and ribavirin is more likely among carriers of rs12979860 C/C and rs8099917 T/T, which might underlie their high rates of SVR.

Thus, *IL28B* polymorphisms did not influence SVR in easy-to-treat patients, such as those with genotype 2/3, rapid virologic responders, and those with acute hepatitis C. While the genetic fingerprint for progression of fibrosis remains elusive, *IL28B* polymorphism predicts SVC and SVR. However, nearly half of the patients achieving an SVR did not have a favorable genotype. Further genetic signals need to be identified to complete the puzzle of factors influencing hepatitis C.

IL28B polymorphisms and DAAs

Several studies have investigated whether *IL28B* polymorphisms have an impact on response rates to triple PEG-IFN, ribavirin, and DAA therapy.

Boceprevir

The SPRINT-2[62] trial tested the efficacy of triple PEG-IFN, ribavirin, and boceprevir therapy in treatment-naïve patients with HCV genotype 1 and investigated the impact of *IL28B* polymorphisms on response rates. The SVR rate in patients with the *IL28B* CC genotype and treated with dual PEG IFN/ribavirin therapy was 78%, and was very similar to the SVR rates observed in patients with the CC genotype receiving triple therapy (80%). However, a dramatic increase was seen in patients with the TT genotype, whereby SVR rates increased significantly from 27% in patients treated with combination PEG IFN/ribavirin therapy to 59% in patients receiving triple therapy; a statistically significant increase in SVR rate was also seen in those with the CT genotype (28% versus 71%, respectively). In other words, patients with nonfavorable *IL28B* genotypes were those who experienced significant improvement in SVR rates with the addition of boceprevir.

The RESPOND-2 trial (ClinicalTrials.gov registry number, NCT00708500) investigated the response of 106 treatment-experienced patients to triple therapy with boceprevir. A significant improvement in SVR rates was observed for all *IL28B* genotypes when boceprevir was added to PEG-IFN/ribavirin therapy. The SVR rate increased from 46% to 77% in those with the CC genotype, from 17% to 73% in those with the CT genotype, and from 50% to 72% in those with the TT genotype.[62]

Telaprevir

A trial comparing the efficacy of triple PEG-IFN/ribavirin/telaprevir therapy with that of combination PEG-IFN/ribavirin therapy showed that SVR rates increased significantly in carriers of the CC genotype from 64% on dual therapy to 90% on triple therapy.[95] An improvement in SVR rates was also observed in patients with the CT genotype (from 25% to 71%) and the TT genotype (from 23% to 73%). Similarly,

the PROVE-2 trial[96] demonstrated enhanced SVR rates in treatment-naïve patients with any *IL28B* genotype, including the TT genotype.

The REALIZE trial (ClinicalTrials.gov registry number NCT00703118)[97] showed that triple PEG-IFN/ribavirin/telaprevir therapy in treatment-experienced patients achieved a significant increase in SVR rates over the standard of care in all *IL28B* genotypes (from 29% to 79% for CC, 16% to 60% for CT, and 13% to 61% for TT). A meta-analysis of five studies including 1,641 patients treated with a triple regimen including telaprevir in four studies and boceprevir in the remaining study demonstrated that addition of a DAA to the PEG-IFN and ribavirin standard of care significantly improved the SVR rate across all *IL28B* genotypes. In addition, patients with the CC genotype had higher SVR rates than those with the CT or TT genotype, regardless of whether patients were naïve, nonresponders, or relapsers.[98]

Furusyo et al[99] focused on the impact of the rs8099917 SNP on the response to triple therapy (with telaprevir being the DAA), and concluded that patients with the TT allele had significantly higher SVR rates than those with the TG or GG allele. All these patients had HCV genotype 1.

Simeprevir

The impact of *IL28B* polymorphism on response to triple therapy with simeprevir among treatment-naïve patients was investigated in a subset of patients enrolled in the PILLAR trial,[65] which focused on the rs12979860 SNP. Addition of simeprevir resulted in significantly improved SVR rates in all *IL28B* genotypes when compared with combination PEG-IFN/ribavirin therapy. SVR rates improved from 18% to 88% in those with the CC genotype, from 31% to 74% in those with the CT genotype, and from 14% to 61% in those with the TT genotype. Among patients with non-CC genotypes, SVR24 rates were generally higher for patients treated with simeprevir 75 mg and 150 mg versus the placebo control. SVR rates with simeprevir 75 mg were 83.9%, 78.1%, and 50.0%, and with simeprevir 150 mg were 97.1%, 80.0%, and 66.7%, respectively, for the CC, CT, and TT genotypes.

Sofosbuvir

The relationship between *IL28B* polymorphisms and response to triple PEG-IFN/ribavirin-sofosbuvir therapy in treatment-naïve patients with HCV genotype 1 was investigated in the NEUTRINO trial (ClinicalTrials.gov registry

number NCT01641640).[60] The SVR rate in carriers of the *IL28B* CC genotype was 98% and among carriers of the non-CC genotype was 87%.[69]

IL28B genotyping is critical when considering triple therapy because DAAs are expensive and have many side effects. *IL28B* genotyping can help physicians to decide whether triple therapy is necessary or if standard of care would be sufficient. Ahlenstiel et al[100] suggest that triple therapy would be more beneficial for patients with the *IL28B* nonresponder genotype, but the role of *IL28B* polymorphisms may diminish with the development of newer and more effective DAAs. Genotyping HCV patients for *IL28B* polymorphisms may be an important cost-effective screening method prior to triple therapy. Patients with a responder genotype can be assigned to treatment with PEG IFN/ribavirin. Retreatment with triple therapy should be considered in the event of relapse. Patients with nonresponder genotypes should be encouraged to start a triple therapy regimen. Null responders constitute a challenge because DAAs do not significantly improve response rates in this population and these patients should wait until more effective DAAs are developed.

Role of *IL28B* in the outcome of a IFN-free regimen

The predictive role of *IL28B* was assessed in 83 patients with chronic hepatitis C assigned to either mericitabine (500 mg or 1,000 mg twice daily) plus danoprevir (100 mg or 200 mg every 8 hours, or 600 or 900 mg twice daily) or placebo. At day 14 (the end of IFN-free treatment), the mean reduction in serum HCV RNA levels was slightly greater in patients with the CC polymorphism ($5.01 \log_{10}$ IU/mL) than in those without ($4.59 \log_{10}$ IU/mL). Modeling showed that patients with the CC polymorphism had slightly better early viral kinetics. Patients with CC also had a better on-treatment response, suggesting that the *IL28B* genotype has a positive influence on early viral kinetics in patients with chronic hepatitis C receiving IFN-free treatment.[66]

IL28B polymorphisms in HCV/HIV coinfection

Several studies[101–109] have genotyped *IL28B* variants in patients coinfected with HCV and HIV. De Araujo et al[101] demonstrated a strong association between the G allele and treatment failure. In contrast, the rs8099917 TT genotype was a strong predictor of treatment success, independent of baseline plasma HCV RNA loads or liver histology. This association was strongly evident in patients with genotype 1 but less obvious in patients with genotype 3. In patients

coinfected with HIV and HCV treated with PEG-IFN and ribavirin, the *IL28B* CC genotype was detected in 75% of those with an SVR.[101–108] The effectiveness of PEG-IFNα-2a in decreasing HCV RNA was greater during the first week of treatment in patients with the CC genotype than in those with the TT/TC genotype (for both genotype 1 and 3). Further, the second slower phase of viral decline was longer for genotype CC than for genotype TT/TC in patients with genotype 1. The rs8103142 CT, rs12979860 CT, and rs11881222 AG genotypes were associated with a decrease in HCV clearance.[101]

In a cohort of HIV-1-infected Europeans recently infected with HCV, Clausen et al[103] reported spontaneous resolution in 23% of patients and chronic evolution in 77%. The exonic rs8103142 CT genotype, the intronic rs11881222 AG genotype, and the haplotype block TCG CTA were associated with persistence of HCV. A significant difference in HCV RNA levels was found between rs8103142 and rs12979860 in individuals with chronic HCV genotype 1. Individuals with chronic HCV genotype 3 and with the favorable haplotype block CTA CTA had higher median HCV RNA levels than those with unfavorable haplotype blocks. Medrano et al[106] developed and validated a noninvasive index including *IL28B* SNP rs12979860, liver stiffness, HCV genotype, and viral load to predict SVR in patients coinfected with HCV and HIV.

IL28B polymorphism and liver transplantation

Fukahara et al[110] investigated whether recipient and donor genetic factors could predict the host response to PEG-IFN/ribavirin therapy in the event of recurrent HCV infection. *IL28B* polymorphism (SNPs rs12980275 and rs8099917) was examined in HCV-infected recipients and donors. A strong association was found between rs8099917 and SVR. Intrahepatic expression of *IL28* messenger RNA was significantly lower in recipients and donors who carried the minor alleles (T/G or T/T) for rs8099917 (P=0.010 and P=0.009, respectively). *IL28B* polymorphism in the donor and recipient and HCV RNA mutation were good predictors of response to treatment. Another study[111] examined rs12979860 C>T SNP in patients with liver graft reinfection. Peak serum alanine aminotransferase and HCV RNA concentrations were higher in patients with the rs12979860 CC donor genotype than in those with the CT/TT genotypes. There were associations between donor *IL28B* rs12979860 CC versus CT/TT and rapid virologic response, complete early virologic response, and SVR, but these were not very strong.

Relationship between other SNPs and outcome of treatment for chronic HCV

Several recent studies have investigated the impact of various SNPs and the outcome of treatment for chronic HCV. One study[112] demonstrated a strong association between SNPs in the inosine triphosphate pyrophosphatase gene and ribavirin-induced hemolytic anemia in patients coinfected with HCV and HIV who were treated with PEG-IFN and ribavirin. Another study[113] investigated the relationship between rs738409 PNPLA3 and development of hepatocellular carcinoma after antiviral therapy comprising PEG-IFN and ribavirin in Japanese patients with HCV serotype 1 and a high viral load.

Pharmacogenomics and future HCV therapies

Recent studies have suggested that PEG-IFN and ribavirin are likely to be supplanted soon by the addition of specifically targeted antiviral therapy for HCV (STAT-C). Resistance to new antivirals such as HCV protease inhibitors and emergence of potentially resistant strains of HCV are likely to develop. It is important to investigate the impact of the patient's genetic make-up on the response to STAT-C and development of resistance or emergence of adverse events. It is thus important to test the efficacy of various emerging antiviral combinations in various geographic areas, ethnic groups, HCV genotypes, and different stages of HCV infection. Stratifying patients enrolled in ongoing clinical trials according to IL-28B variations will help in tailoring future triple therapies.

Pharmacogenomics in HCV infection: benefits and barriers

Pharmacogenomics is a promising emerging field that provides insight into the impact of genetic variations on response of HCV patients to therapy. Pharmacogenomics offers potential clinical benefits to patients and economic benefits for health care delivery. This is crucial in the era of triple therapies and IFN-free regimens. DAAs are not only expensive but are genotype-specific and associated with development of resistance. Identifying individuals with a high chance of achieving an SVR will avoid failure of therapy and generation of unnecessary costs. Likewise, identifying chronic HCV patients at risk of accelerated liver fibrosis or development of hepatocellular carcinoma will help in prioritizing therapy for those patients to halt disease progression and prevent cirrhosis. Knowing upfront whether an individual may develop resistance to a DAA-containing regimen will enable the physician

to select the appropriate therapy according to the needs of a specific patient. From the public health standpoint, treatment of acute infection will reduce the risk of transmission and prevent evolution of chronic disease.

Despite the advantages of pharmacogenomics in improving the outcome of HCV infection, several barriers and ethical concerns may delay the adoption of treatment algorithms based on genetic profiling of patients with HCV. Detecting gene variations is a somewhat complicated and expensive process that might not be easily available in developing countries with a heavy burden of HCV. Simpler affordable tests for detecting genetic variations are thus required to maximize the benefit of this technology.

To date, a limited number of drugs are approved for the treatment of chronic HCV infection. Thus, patients with gene variations associated with inadequate response may have no alternatives for treatment, leading to ethical concerns and debate. Would health insurance companies cover the costs of extra diagnostic genetic steps to determine eligibility for therapy? If a patient had an unfavorable genotype but other favorable pretreatment host and viral factors, would he or she be denied therapy and excluded from health insurance? If pretreatment genetic testing suggested that a particular individual had a high predisposition to adverse events, should this patient be denied treatment? Is pre-emptive treatment of adverse events possible or justified? What about the psychologic harm that may result from depriving an individual of treatment? Despite the potential role played by the individual's genetic make-up in determining the outcome of HCV infection, variation in drug response is not limited to micropolymorphisms or genes. Other host, viral, and environmental factors are likely to affect the safety and efficacy of therapy in particular individuals.

Requesting various genetic tests for different population subsets will undoubtedly complicate the process of drug prescribing. This complexity will require cooperation between disciplines to individualize health care. It is necessary for health providers to become more knowledgeable about the scope and limitations of genetic testing to be able to interpret results accurately and make informed decisions based on clinical factors as well as SNP genotyping. Health providers also need to reach out and communicate with their patients to clarify the impact of genes on response to therapy.

HCV and pharmacogenomics in developing countries

Pharmacogenomic applications may be important tools for individualizing the therapeutic options for HCV, restricting HCV transmission, halting the progression of chronic hepatitis, and ensuring that treatment is cost-effective. However, several questions persist. Should developing countries continue to act as end users for technology rather than be developers and innovators? The wide applications of pharmacogenomics seem an adequate setting for this argument, particularly in developing countries with a high prevalence of HCV and limited resources. Egypt could be a good candidate for pharmacogenomic applications in the field of HCV despite numerous challenges. The Egyptian government subsidizes the majority of health care services for HCV patients and failure to achieve an SVR represents wasted resources. Thus, prediction of treatment response seems a realistic approach to prioritize therapy for patients who are likely to respond.

In conclusion, pharmacogenomics offers the potential to tailor HCV therapy to increase the effectiveness of existing and new therapies, minimize adverse events, and maximize the cost-benefit of health interventions for this infection, given its vast impact on public health globally. Emerging data suggest that treatment for HCV could be individualized according to the genetic profile of the patient, pretreatment host, viral characteristics, and viral kinetics on treatment. As genomics technology becomes more common in both developed western countries and low-income to middle-income countries, the landscape of health care services and delivery will also change, with equitable and timely genomics applications for diseases such as HCV infection affecting the global society.

Disclosure

The author reports no conflicts of interest in this work.

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