Viral and host factors associated with outcomes of hepatitis C virus infection (Review)

ZEHUI YAN and YUMING WANG

Department of Infectious Diseases, Southwest Hospital, Third Military Medical University, Shapingba, Chongqing 400038, P.R. China

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Abstract. Hepatitis C virus (HCV) infection is a major health issue globally. Owing to the progress made in host genetics and HCV molecular virology, emerging data have suggested that the natural course and treatment response in patients with HCV infection are largely determined by complex host-viral interactions. HCV genotype is the most important viral factor predicting the response to pegylated interferon-α plus ribavirin therapy. The subtype of HCV genotype 1 is the key viral factor that predicts the efficacy of direct-acting antiviral therapy. HCV genome heterogeneity and baseline viral load are additionally associated with the treatment response. Multiple host genetic variants localized in genes associated with the immune response have been identified as predictors of spontaneous disease course and therapy outcome in chronic HCV. However, most findings from candidate gene association studies have not been proven universal for all investigated populations and independent studies. Previous findings in independent large genome wide association studies confirmed that interferon-λ3 gene polymorphisms are associated with spontaneous clearance and treatment responsiveness. A polymorphism of the inosine triphosphatase gene has been identified as a protective factor against ribavirin-induced anemia and dose reductions. Another genetic variant in the patatin-like phospholipase domain containing 3 genes is associated with hepatic steatosis and fibrosis in patients with HCV. The present review focused on the identified viral and host factors associated with outcomes of patients with HCV, and assessed the involvement of viral and host genetics in the natural history and treatment outcomes of HCV infection. This will provide novel ideas concerning personalized prevention and individualized clinical management.

Correspondence to: Professor Yuming Wang, Department of Infectious Diseases, Southwest Hospital, Third Military Medical University, 30 Gaotanyan Street, Shapingba, Chongqing 400038, P.R. China
E-mail: wym417@163.com

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1. Introduction

Hepatitis C virus (HCV) is a health issue affecting >170 million people globally (1). The natural course of HCV infection is variable, demonstrating heterogeneity among different individuals. Following acute infection <30% patients will spontaneously clear the virus, while >70% patients will develop persistent, chronic HCV infection (2). The most severe results of chronic infection are cirrhosis, hepatic decompensation, liver failure and hepatocarcinoma, with HCV infection ultimately causing ~350,000 deaths per year (3). The identification of viral and host factors that impact disease progression may facilitate understanding of the mechanisms underlying chronic HCV infection.

At present, no effective vaccine is available for HCV. For over a decade, the standard treatment of chronic HCV infection has been based on the combination of subcutaneous pegylated interferon-α (Peg-IFN-α) and oral ribavirin (RBV) for 24 or 48 weeks, resulting in sustained virologic response (SVR) in 40-50% of patients with genotype 1, and ~80% in those infected with genotype 2/3 (4,5). However, this treatment is associated with clinically significant adverse events, and is poorly tolerated and less efficacious in patients with advanced disease (6). The introduction of direct-acting antiviral drugs (DAAs), with two nonstructural protein (NS) 3/4A protease inhibitor (PI) drugs licensed in 2011, has increased the number of patients who respond to treatment, marking a novel era for HCV treatment. At present, >40 novel NS3/4A, NS5A, or NS5B protease inhibitors are in development. These agents achieve high cure rates when combined with Peg-IFN-α+RBV treatments, and demonstrate promising clinical results when administered in all-oral combinations (7). However, these DAA regimens are poorly tolerated, are associated with a high pill burden and an inconvenient dosing frequency, and

are not recommended for all patients. The limited efficacy and expensive cost of antiviral therapy, combined with the unfavorable toxicity profile, has additionally inspired interest in determining viral and host predictors of HCV outcomes.

Owing to advances in sequencing technology and clinical progress, emerging data have suggested that the natural course and treatment response in patients with HCV infection are primarily determined by the complex interactions between host and virus (8-10). The present review summarizes the viral and host genetic factors associated with the clinical outcome of patients with HCV infection, and assesses the involvement of these predictors in the natural history of HCV infection and its treatment outcomes. A full understanding of the significance of these biomarkers may allow an enhanced understanding of the pathophysiology of chronic HCV infection, and provide novel ideas regarding personalized prevention and the individualization of clinical management.

2. Viral factors associated with the clinical outcome of HCV infected patients

Viral factors and natural history of HCV infection. An early systematic review (2) suggested that no significant association existed between HCV viral factors and spontaneous HCV clearance. However, a previous study suggested that the outcome of HCV infection is primarily controlled by two sequential viral bottleneck events, irrespective of subsequent clearance or chronicity (11). The first bottleneck was associated with transmission, with only one to two viruses successfully establishing infection in most cases. The second bottleneck occurred following 100 days, and exhibited a decreasing viral diversity. To assess independent viral predictors for fibrosis progression, Bochud *et al* (12) identified 1,189 patients infected with HCV with >1 live biopsy prior to infection and antiviral treatment. The ratio of fibrosis METAVIR score to duration of infection was used to assess the stage-constant fibrosis progression rate, using a Markov model. Univariate and multivariate regression analysis confirmed that HCV genotype 3 was associated with the increased risk of fibrosis progression. This notable result may provide novel ideas regarding the management of individuals infected with HCV genotype 3.

Viral factors on treatment response

HCV genotype. HCV genotype is the most important viral factor predicting the response to Peg-IFN-α+RBV therapy. In treatment-naïve individuals, Peg-IFN-α+RBV treatment achieves SVR rates of 40-50% in HCV genotype 1 infection, compared with 75% in genotypes 2 and 3 infection (13). Data from other clinical trials additionally suggests that the SVR of patients with genotype 1/4/5/6 infection is reduced compared with individuals with genotype 2/3 infection (14). Treatment with Peg-IFN-α+RBV may therefore be individualized by genotype. A previous randomized study suggested that patients infected with genotype 1 HCV should receive Peg-IFN-α-2a+RBV treatment for 48 weeks, whereas patients with genotypes 2/3 should only be treated with Peg-IFN-α-2a+RBV for 24 weeks (15). Furthermore, a meta-analysis of six randomized trials suggested that Peg-IFN-α+RBV combination treatment, administered for 48 weeks, is the optimal regimen for patients infected with HCV genotype 4 (16). A further retrospective study suggested that treatment with Peg-IFN-α+RBV for 48 weeks was effective and preferable to treatment for 24 weeks for patients infected with HCV genotype 6 (17). Due to the limited global infection rate of HCV genotype 5, data to make recommendations on the specific doses or durations of treatment with Peg-IFN-α+RBV for patients infected with HCV genotype 6 remains insufficient at present.

HCV genotype and subtype remains important in determining the appropriate antiviral treatment regimen during the present era of DAAs. Telaprevir and boceprevir are first generation HCV PIs, and have specificity for HCV genotype 1. These PIs are effective against HCV genotypes 2/6, but demonstrate insufficient activity against HCV genotypes 3/4/5 (18,19). A previous study demonstrated that the combination of Peg-IFN-α+RBV with telaprevir increased SVR to 69-75%, whereas the SVR of patients with Peg-IFN-α+RBV standard therapy was 44% (20). Furthermore, telaprevir treatment also demonstrated increased efficacy in patients with HCV genotype 1 who had previously failed to improve under Peg-IFN-α+RBV treatment (21). Similarly, among treatment-naïve patients with HCV genotype 1, boceprevir improved SVR from treatment with Peg-IFN-α+RBV alone from 40% to 67-68% in patients not of African descent, and from 23% to 42-53% in patients of African descent (22). Among treatment-experienced patients, previous relapsers had a SVR rate of 75% when treated with boceprevir, compared with 29% from Peg-IFN-α+RBV alone, whereas partial-responders increased the SVR rate from 7 to 52% (23). Even for the null responders to Peg-IFN-α+RBV treatment, boceprevir therapy achieved an SVR rate of 38% (24). Overall, telaprevir and boceprevir increase the SVR rate in HCV genotype 1 infection, and the results are comparable to Peg-IFN-α+RBV regimens in genotype 2/3 infection. With the advancement of pan-genotypic DAAs, combination treatment with different DAAs is expected to achieve similar antiviral activity against different HCV genotypes in the future (25,26). GS-7977/sofosbuvir (nucleotide inhibitors of the HCV NS5B polymerase), daclatasvir (NS5A inhibitor) and MK-5172 (the second-generation PIs) have all demonstrated pan-genotypic antiviral effects. A previous study demonstrated that sofosbuvir combined with RBV achieved an 84% SVR rate in patients infected with HCV genotype 1, and 100% in patients infected with genotype 2/3 (27). Simeprevir is an NS3/4A protease inhibitor approved for treatment of HCV genotypes 1 and 4. A previous study additionally confirmed the efficacy and safety of simeprevir with Peg-IFN-α+RBV in treatment-naive or -experienced patients, and achieved satisfactory results (28).

The subtype of HCV 1 genotype is a key viral factor that predicts the efficacy of direct-acting antiviral therapy (10). When patients were treated with a DAA-containing regimen individuals infected with genotype 1a had ~10% lower rates of response compared with patients with infected with genotype 1b (29,30). The differences in SVR rate may be due to the genetic barrier to resistance. The subtype of HCV 1 genotype is also a response predictor to IFN-free regimens. A previous study used triple oral therapy [nucleos (t)ide inhibitors (NI)/PI/RBV] to treat patients infected with genotype 1 and demonstrated that week 12 SVR was 38-47% in patients infected with HCV subtype 1a, improving to 63-83% in patients infected with

HCV subtype 1b (29). Another study additionally assessed the combination of daclatasvir and asunaprevir among treatment-experienced, genotype 1-infected non-responders without cirrhosis, randomly assigned to treatment with or without Peg-IFN-α+RBV, and demonstrated that all patients infected with genotype 1b achieved an SVR, while only 2/9 patients infected with genotype 1a achieved an SVR (30). Further analysis revealed that the HCV genome in failed treatment exhibited variations which may have resistance to NS5A and NS3 inhibitors (10).

Pretreatment viral load. Multivariate analyses from multiple studies regarding different populations have suggested that pretreatment viral load, irrespective of the HCV genotype, is an independent viral factor to predict the SVR (31-33). SVRs were increased in individuals with a low HCV RNA concentration of <600,000-800,000 IU/ml. However, the influence of the alterations in viral load range on the SVR was not linear. When the viral load was <400,000 IU/ml, a decrease in the amount of HCV increased the SVR rate. Nevertheless, when the pretreatment viral load was >400,000 IU/ml, the impact of the variable viral load on the SVR was insignificant (34,35). The European guidelines for the prevention and treatment of hepatitis C reported that when the pretreatment HCV RNA concentration was <400,000-800,000 IU/ml, it was possible to shorten the treatment duration for HCV genotype 1/4 in treatment-naïve patients who achieved a rapid virological response to 24 weeks, and to 12-16 weeks for patients infected with genotype 2/3 (36,37). However, it should be emphasized that the viral load must be determined by a sensitive, quantitative assay.

HCV genetic mutation. HCV demonstrates enormous genetic diversity in infected individuals, existing in the blood as a collection of related quasi-species. There is ~10% difference between the genomic sequences among independent HCV isolates. Owing to advances in HCV molecular virology and progression in sequencing techniques, emerging data have suggested that certain HCV gene mutations have additionally impacted the SVRs of individuals infected with HCV.

Previous reports have identified an association between the Peg-IFN-α+RBV treatment response and amino acid substitutions in domain 2 of the NS5A region. These include the interferon sensitivity determining region (ISDR; aa2,209-2,248), the protein kinase R (PKR)-binding domain (aa2,248-2,274), the V3 region (aa2,334-2,356) and the interferon ribavirin resistance determining region (aa2334-2379) (38). Data from Japanese populations infected with HCV-1b indicated that an increased heterogeneity of the HCV genome was associated with increased SVRs of Peg-IFN-α+RBV treatment (39-42). However, these observations have not been reproduced in other countries.

Numerous studies have additionally reported an association between the Peg-IFN-α+RBV treatment response and amino acid variations in the HCV core region at positions 70 and 91 (Core70) (43,44). To establish a predictive model based on the combined effect of ISDR and Core70 variations on SVR, a previous study collected and analyzed the data from 304 patients and revealed that ISDR and Core70 variants with traditional baseline factors enhanced the pretreatment SVR prediction and resulted in 94% of the variability in SVR (38). Furthermore, it has been reported that the variants at HCV Core70 are associated with the response to telaprevir-based therapy; however, this study only used a small cohort (45).

To investigate the contribution of genome-wide HCV genetic variations on treatment outcomes, Donlin *et al* (46) determined the near-full length pre-therapy consensus sequences among 94 patients infected with genotype-1a/b and observed that HCV sequences from individuals who achieved SVR were more diverse than those from non-responders. These differences were primarily identified in the NS5A region in genotype 1a and in the core and NS2 in genotype 1b. Host selection pressures were unable to explain these inter-patient diversity differences. Increased inter-patient viral genetic diversity was correlated with successful treatment, implying that there are HCV genotype 1 strains with intrinsic differences in sensitivity to therapy. Individuals infected with genotype 1b had viral genetic differences that correlated with treatment outcome (47).

The rapid replication rate of HCV, along with its error-prone polymerase, results in the generation of mutations throughout the viral genome and, thus, naturally occurring resistance-associated variants (RAVs) (48). RAVs are selected within days of DAA mono-therapy, resulting in virologic breakthrough (49). Mutations of Arg155 have been demonstrated to confer broad cross-resistance to all first generation inhibitors. Conversely, mutations of Val36 or Thr54 have been observed exclusively in association with covalent linear inhibitors, and mutations of Asp168 have been specifically demonstrated to confer mutation to noncovalent peptidomimetic inhibitors (7). Previous studies have demonstrated that combination with PEG-IFN/RBV treatment is able to prevent these emerging mutants (50,51), thus current PI regimens involve triple therapy with Peg-IFN-α+RBV. Notably, there are different genetic barriers regarding DAA resistance between HCV 1a and 1b. For example, selection of the HCV R155K variant, a common telaprevir-resistant variant, requires two nucleotide alterations in HCV 1b but one nucleotide variant for HCV 1a. Resistance-associated polymorphisms have additionally been determined for NS5A, NS5B and cyclophilin inhibitors (52). Sofosbuvir is notable for its low genetic barriers of resistance. The S282T variant exhibits a resistance-associated variant *in vitro* and has poor replication fitness; however, the S282T variant remains to be observed clinically, even in the setting of monotherapy. The reasons for the differential effect of the S282T variant *in vitro* and *in vivo* remains unclear; however, monotherapy is not effective due to high rates of relapse post-therapy. Sofosbuvir monotherapy has not been used to treat patients with HCV genotype 1 (7).

3. Host factors associated with outcome of HCV infected patients

Host factors and spontaneous clearance

Discovery from genome-wide association studies. To determine host genetic polymorphisms associated with HCV spontaneous clearance, in 2009, Thomas *et al* (53) conducted a genome-wide association study (GWAS) in an international, multicenter cohort study including 388 patients with spontaneous HCV clearance and 620 patients with persistent HCV infection. They observed that the IFN-λ3 (*IL28B)* rs12979860CC genotype was

significantly associated with HCV spontaneous clearance among individuals of European and African ancestry. Rauch *et al* (54) performed another GWAS to screen for host genetic variants associated with persistent HCV infection. The study was comprised of 1015 patients with chronic hepatitis C and 347 individuals who spontaneously cleared the virus, among which 448 were co-infected with human immunodeficiency virus (HIV). A total of 7 single nucleotide polymorphisms (SNPs) in the *IL28B* gene were associated with HCV clearance. The *IL28B* rs8099917 variant was demonstrated to have the strongest genetic effect associated with persistent HCV infection. The favorable genotype of *IL28B* rs8099917 polymorphism has ~2-fold increased odds of spontaneous clearance. The risk allele of this variant was identified in 24% of individuals who spontaneously cleared the virus, 32% of patients with chronic infections who responded to antiviral treatment, and 58% who failed to respond to therapy. Furthermore, the association was observed not only in individuals infected with mono-HCV, but additionally in patients co-infected with HCV/HIV. The association of the *IL28B* polymorphisms with the outcome of HCV infection infer the importance of innate immunity and IFN λ in the pathogenesis of HCV infection, and indicted the involvement of *IL28B* in HCV spontaneous clearance.

Jaundice is relatively uncommon in patients with HCV, and the inter-individual differences noted in single source outbreaks support the viewpoint that host factors influence the competence of the immune response to acute HCV (55). *IL28B* variants have additionally been determined to be associated with symptomatic jaundice in acute HCV infection in an Australian (56) and a German cohort (57). In the Australian trial, Grebely *et al* (56) revealed that HCV seroconversion diseases with jaundice was the only predictor of HCV spontaneous clearance by Cox proportional hazards analysis (without the *IL28B* genotype), while *IL28B* rs8099917 TT homozygosity (versus GT/GG) was the only factor independently predicting time to spontaneous clearance (with the *IL28B* genotype). Patients with jaundice were more frequently rs8099917 TT homozygotes than other genotypes (GG/GT). These findings suggested that *IL28B* genetic variations were associated with spontaneous clearance but not treatment-induced clearance in patients with acute HCV infection. Tillmann *et al* (57) additionally revealed that the *IL28B* rs12979860 variant was significantly associated with jaundice and acute clearance of HCV. In this study, spontaneous clearance of acute HCV was more common in individuals with the *IL28B* rs12979860 C/C genotype than in non-C/C patients (with T/T or C/T). Similarly, jaundice during acute HCV infection was more common in patients with the C/C genotype compared with C/T or T/T. In individuals with the *IL28B* C/C genotype, no historical link was observed between jaundice and acute clearance of HCV. In contrast, among patients with a non-C/C genotype, jaundice was associated with an increased chance of spontaneous clearance (42.9%) compared with those without jaundice (13.7%). These results suggested that individuals with the *IL28B* non-CC genotype who did not develop jaundice were less likely to achieve spontaneous clearance, and thus may benefit from early therapeutic intervention.

Data from candidate gene association studies. Prior to the discovery of the historical link between *IL28B* genetic variants and the outcomes of HCV infection by means of GWAS, the candidate gene approach was used to identify host genetic factors associated with susceptibility to or spontaneous clearance of HCV. Candidate gene association studies based on gene function, and innate and adaptive immune signaling pathways have postulated that interleukins (ILs), chemokines, human leukocyte antigen (HLA), killer-cell immunoglobulin-like receptors (KIR) and cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*) affect the natural history of HCV infection (8). However, the data from most of these candidate gene association studies have not been proven universal for all investigated populations and independent studies.

i) Cytokine genes. Cytokines represent a large family of molecules, including ILs, IFNs and members of the tumor necrosis factor (TNF) family. They are involved in the initiation and regulation of immune responses, and therefore may affect susceptibility to and/or the natural course of HCV infection.

As a multifunctional cytokine, IL-6 is involved in the stimulation of hepatocytes to produce acute-phase proteins (58), liver regeneration and protection against hepatic injury (59). Previous studies have reported that carriers of an *IL-6* low producer genotype (174C/C) had an increased viral clearance rate compared with individuals with the high producer genotype (174 G/G and 174 G/C) (60,61). However, the association between *IL-6* polymorphisms and the outcome of HCV infection was not confirmed by other studies (62). Two loci (rs6693899 and rs6703630) in the promoter region of the *IL-10* gene were identified to be associated with the levels of IL-10 production, and have a significant association with the persistence of HCV infection in African Americans, exclusively (63). Other previous studies assessed the relevance of functional *IL-10* gene variants in hepatitis C and revealed that the *IL-10* high-producer genotype (1082 G/G) is associated with a higher rate of HCV clearance (64,65). However, these data remain controversial in different independent studies (61-63,65-67). IL-12 is a pivotal mediator in the generation of Th1 antiviral cellular immune responses. Several previous studies additionally analyzed whether the *IL-12B* genetic variants within the promoter region (4 bp insertion/deletion) and the 3'-untranslated region (UTR; +1188A>C), which have been proposed to regulate IL-12 synthesis, were associated with the natural course of hepatitis C and treatment outcome (68-70). Houldsworth *et al* (68) demonstrated that patients with chronic infections were significantly more likely to be homozygous for the +1188A allele than those with a resolved HCV infection. In contrast, a study by Mueller *et al* (69) observed no historical link between *IL12B* genetic variants and self-limited HCV infection. IL-18 is a key cytokine in the Th1/Th2-driven immune response. Two polymorphisms (-607C>A and -137G>C) in the promoter of the *IL-18* gene and the corresponding haplotype have been demonstrated to have a significant association with HCV clearance among injection drug users (71). In addition, allelic variants in *IL-22* (72) and *IL19/20* have been suggested to be involved in the outcome of hepatitis C infection.

TNF-α has been reported to be involved in immunopathogenesis during acute and chronic HCV infection, viral persistence and the response to IFN-α based therapy (73).

Genetic variants in the *TNF-α* promoter region, including mutations at positions 308G>A and 238A>G, have been demonstrated to influence expression of TNF-α (74-76). However, whether these polymorphisms affect the pathogenesis and progression of chronic HCV infection and/or the response to IFN-α therapy remains to be elucidated, as conflicting data have been reported (77-80). TGF-β is involved in the control of growth, differentiation, and apoptosis of cells. The rare allele of a variant (509T>C) in the promoter region of the *TGF-β1* gene has been confirmed to be linked with increased HCV clearance rates (81).

ii) HLA. Cell-mediated immunity is considered to be an important mechanism for resolution of primary HCV infection (82). T-cell-mediated immunity involves cluster of differentiation (CD)8+ cytotoxic T lymphocytes (CTLs) and CD4+ T-helper lymphocytes, which recognize viral peptides bound to HLA class I and II molecules, respectively (83).

Multiple previous studies have analyzed the relevance of *HLA* alleles in HCV and identified specific *HLA* alleles that affected the outcome of HCV infection However, data regarding potential associations between the HLA system and the outcome of HCV infection are conflicting and suggest major influences from other factors not associated with HLA alleles (84,85). In a single Irish cohort, the *HLA-I* alleles *A3*, *B27* and *Cw*01* were identified to have significant associations with HCV clearance, while *B8* was ascertained to be associated with persistent HCV infection (86). In two heterogeneous cohorts, *HLA-B57* was revealed to be significantly associated with HCV clearance in patients of different ethnicity, including Caucasians, African Americans and West Africans (87,88). Furthermore, a large scale study in liver transplant recipients provided evidence supporting a major histocompatibility complex, class II, DRβ1 (*HLA-DRB1*) heterozygote advantage against HCV infection (89). With respect to *HLA-II* polymorphisms, a meta-analysis suggested that specific *HLA-II* alleles affected the natural course of HCV infection. *HLA DQB1*0301* and *DRB1*1101* were demonstrated to be protective alleles and to present HCV epitopes more effectively to CD4+ T-lymphocytes than to others (90).

iii) KIR. Natural killer cells, as key components of the innate immune system, are involved in host defenses against viral infection by using inhibitory and activation receptors, including KIRs (91). Evidence is emerging from disease-association studies that KIR receptors may serve beneficial functions in HCV infection (92-95).

The killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (*KIR2DL3*) gene is an inhibitory receptor gene involved in the innate immune response. Several studies have examined the effect of *KIR2DL3* variants on spontaneous HCV resolution. Khakoo *et al* (92) reported that genes encoding KIR2DL3 and HLA-C1 directly affected spontaneous HCV clearance in patients infected with low-dose HCV RNA, but not in patients infected with high concentration HCV RNA. These findings have been confirmed in other independent studies (93,94). As almost all studies observed that the effect of *KIR* variants on spontaneous HCV clearance is weaker than that of the *IL28B* genotype, a notable study from Dring *et al* (95) synergized the effect of *KIR* variants and *IL28B* genotype, and demonstrated that the patients with markers of *KIR2DS3* and *IL28B* genotypes had a higher chance of maintaining chronic, persistent infection compared with individuals with either marker alone.

Furthermore, *KIR2DL3/HLA-C1* genetic variants additionally have an association with the disease progression of HCV infection. Knapp *et al* (96) analyzed the distribution of *KIR2DL3/HLA-C1* homozygosity in individuals with apparent resistance to HCV infection, who remain seronegative and aviremic despite long-term injected drug use, and additionally patients who successfully cleared HCV with treatment. In this study, homozygosity for *KIR2DL3/HLA-C* allotypes was more frequent in exposed seronegative aviremic individuals compared with those with chronic HCV. The finding that *KIR2DL3/HLA-C1* homozygosity was associated with disease progression of chronic HCV infection, conferring a protective effect, was confirmed by two other studies (92,97); however, two other smaller and ethnically diverse studies failed to verify this protective effect (98,99).

iv) CTLA4. CTLA4 is a co-stimulatory molecule that attenuates T lymphocyte responses and is involved in the resolution of HCV infection. Schott *et al* (100) investigated whether *CTLA4* genetic variants affect the outcome of HCV infection. They examined *CTLA4* polymorphisms -318C>T at the promoter site and +49A>G in exon 1 and revealed that *CTLA4* polymorphisms have a gender-dependent association with the clearance of HCV infection.

v) Apolipoprotein B (ApoB). HCV binds to ApoB and low-density lipoprotein (LDL) prior to entering hepatocytes. *ApoB* promoter polymorphisms influence the levels of ApoB and LDL in the blood. Zhu *et al* (101) investigated the correlations between *ApoB* promoter polymorphism and HCV infection. In this study, the *ApoB* promoter variant at the 516C>T position was suggested to affect susceptibility to and the outcome of HCV clearance. Therefore, the CC genotype of the ApoB promoter at the 516 position may increase susceptibility to HCV infection, and the TT genotype may be associated with viral clearance.

Host factors on treatment response

IL28B polymorphisms and IFN-based therapy. Chronic hepatitis C is difficult to cure and current standard treatment options have variable success rates and considerable adverse effects (102). It has been observed that the Peg-IFN-α+RBV response rates vary with ethnicity; for example, Han Chinese individuals achieve the highest rate of SVR, whereas the SVR rate in African-Americans is <½ that in Caucasians. This inferred that host genetic factors may be involved in the Peg-IFN-α+RBV treatment response. In late 2009 and early 2010, four landmark GWASs reported by four independent groups consistently demonstrated that polymorphisms in the *IL-28B* gene are associated with hepatitis C treatment efficacy (54,103-105).

Ge *et al* (103) were first to examine the potential link between *IL28B* genetic variants and SVR. In their GWAS, a genetic polymorphism (rs12979860 C>T) near the *IL28B* gene was revealed to have a significant association with a ~2-fold increase in response to Peg-IFN-α+RBV treatment, among

individuals of European ancestry and African-Americans. As the frequency of the rs12979860 CC genotype in Europeans, which is associated with improved IFN-treatment responses, is substantially greater than that in African populations, this genetic variant may be able to explain ~½ the difference in response rates among different ethnicities. Three other GWAS focusing on different populations of patients have independently confirmed that *IL28B* genetic polymorphism is an important predictor of the response to Peg-IFN-α+RBV treatment. Suppiah *et al* (104) also performed a GWAS of SVR to Peg-IFN-α+RBV combination therapy in Australian and European individuals infected with HCV genotype 1 and reported an association between SVR and the rs8099917 polymorphism of the *IL28B* gene. An independent Japanese GWAS demonstrated that rs12980275 and rs8099917 variants near the *IL28B* gene were correlated with the treatment response in individuals infected with HCV genotype 1 (105). Following logistic regression analysis, the rs8099917 polymorphism was identified as one of the most important factors predicting failure to respond to therapy. Rauch *et al* (54) studied 1,362 European patients and demonstrated that the minor allele of the rs8099917 polymorphism was associated with non-response to Peg-IFN-α+RBV combination therapy, with the strongest effect observed in individuals infected with HCV genotype 1.

IL28B genetic variants are additionally important predictors of response to therapy for patients infected with HCV genotype 4. Antaki *et al* (106) analyzed the association of *IL28B* polymorphisms with treatment response among treatment-naïve patients infected with HCV genotype 4, all from Syria, and demonstrated that the SVR rates in rs8099917 TT and rs12979860 CC carriers were increased compared with rs8099917 TG/GG and rs12979860 CT/TT carriers. However, the influence of *IL28B* on the treatment response in individuals infected with HCV genotypes 2 and 3 seem less clinically relevant than in individuals infected with HCV genotype 1. This may be due to the fact that the SVRs in patients infected with HCV genotypes 2 and 3, >70% in most studies, are higher than those in patients infected with HCV genotype 1. From 650 HIV/HCV co-infected patients, Rallon *et al* (107) demonstrated that rs12979860 is associated with the HCV treatment response in patients co-infected with HIV and HCV. The CC genotype of the rs12979860 locus was a valuable predictor of SVR to HCV treatment in HIV/HCV co-infected patients; the SVR rate was increased in patients with rs12979860 CC compared with CT/TT genotypes.

Certain studies have demonstrated that improved on-treatment viral kinetics may result in an improved SVR for patients receiving Peg-IFN-α+RBV therapy. Thompson *et al* (108) reported that an *IL28B* genetic variant is associated with improved viral kinetics and is the strongest pretreatment predictor of SVR for patients infected with HCV genotype 1. Bochud *et al* (109) demonstrated that polymorphisms in *IL28B* are significantly associated with viral decline during the early phase of Peg-IFN-α+RBV therapy in chronic HCV infection, irrespective of HCV genotype. However, other studies have observed differences in on-treatment viral kinetics, but did not identify any statistical difference in SVR. Scherzer *et al* (110) examined the effect of two polymorphisms of *IL28B* (rs12979860 and rs8099917) on the early VR of treatment-naïve patients, and demonstrated that these two polymorphisms were not associated with the SVR of patients who did not have genotype 1 by multivariate analysis, including rapid VR data. The patients carrying the genotypes of rs12979860 C/C and rs8099917 T/T appear to have a greater chance of achieving an early VR to Peg-IFN-α+RBV, which may occur as a consequence of their high rates of SVR. Another study (111) focusing on Asian patients additionally demonstrated that the achievement of a rapid VR was the single predictor of SVR in patients infected with HCV genotype 2 patients, whereas the rs8099917 genotypes did not affect SVR with or without rapid VR. Similarly, *IL28B* genotype does not predict the efficacy of treatment for patients with acute HCV infection (112). The negative relationship between the *IL28B* genotype and treatment response in individuals with acute HCV infection may be limited by the smaller size of the cohorts, but also may be due to the fact that the SVR was high when individuals with acute HCV infection were treated as soon as possible (113-115).

The difference in the distribution of the improved treatment response genotype of *IL28B* among individuals from different ethnicities explains much of the recognized ethnic disparity in treatment response rates. The above discoveries represent significant advances, which not only assist the clinical physician in personalizing therapy for patients infected with HCV, but also provide a novel way to research viral pathogenesis and therapeutic development (116). By multivariate regression analysis including multiple viral and host predictors, the *IL28B* genetic variant was verified to be the best predictor of response to Peg-IFN-α+RBV therapy, being more effective than other predictors including ethnic background, baseline viral load, degree of liver fibrosis, fasting glucose level and BMI (108). Halfon *et al* (117) examined the predictive values of rs12979860 and rs8099917 in 198 patients infected with HCV genotype 1 and suggested that the genotype of rs12979860 seemed to be enough for clinical decisions. The European Association for the Study of the Liver guidelines revealed that it is possible to use *IL28B* genetic variants to predict treatment response to DAA regimens, but the predictive value was limited (36). In contrast, the American Association for the Study of Liver Diseases argued that when determining the treatment regimen (Peg-IFN-α+RBV combined regimen with or without DAA), the *IL28B* genotype is a valuable predictor (118).

The association between *IL28B* polymorphisms and the response to IFN-based treatment is biologically plausible, however, the reasons underlying the relationship between the *IL28B* genotype and HCV clearance remains unclear. The *IL28B* gene is located on chromosome 19q13 and encodes a protein known as IFN-λ3 of the interferon family (119,120). *IL28B* is involved in the process of viral resistance and is upregulated by interferons during HCV infection. Previous studies have inferred that there is a link between *IL28B* polymorphism and its expression, as IFN-λ3 expression levels in peripheral blood mononuclear cells of individuals with the minor alleles are lower than those without (104,105), but this conclusion has not been confirmed by other studies (103,121,122). In addition, *IL28B* variants may affect the function of IFN-λ3 protein. *IL28B* polymorphism has been observed to have a significant association with patterns of intrahepatic interferon-stimulated gene (ISG) expression in the hepatic cells (121,122). It has been reported that low expression of hepatic ISGs is correlated with a positive response to IFN-α treatment (121). The good

response *IL28B* genotype is associated with lower levels of intrahepatic ISG expression, suggesting that *IL28B* variants may explain this phenomenon.

IL28B genotype and direct-acting antiviral therapy. The predictive value of *IL28B* genotype is not only limited to the regimen of Peg-IFN-α+RBV therapy, with multiple studies suggesting that *IL28B* polymorphisms are correlated with the response to Peg-IFN-α+RBV treatment combined with DAAs. A study of Japanese patients infected with HCV genotype 1b receiving a triple therapy of telaprevir/Peg-IFN-α+RBV reported that rs12979860 and rs8099917 *IL28B* gene polymorphisms were associated with SVR, and confirmed that rs8099917 was an independent predictor of the SVR of this telaprevir-based triple therapy (45). Similarly, another study reported that a favorable *IL28B* genotype increased the rate of SVR from 59-72% to 87-90% in telaprevir-based triple therapy (123). Furthermore, Bronowicki *et al* (124) reported all patients with *IL28B* CC genotype achieved SVR following treatment with 12 weeks of telaprevir/Peg-IFN-α+RBV triple therapy in the PROVE2 trial. The ZENITH study (125) also reported high SVR rates in patients with favorable *IL28B* genotypes treated with VX-222 in combination with telaprevir/Peg-IFN-α+RBV. Poordad *et al* (126) demonstrated that a favorable *IL28B* genotype improved SVR from 62-68% in Peg-IFN-α+RBV therapy to 80-82% in boceprevir/Peg-IFN-α+RBV triple therapy, where all patients had hepatitis C genotype 1. Faldaprevir is a potent HCV NS3/4A protease inhibitor with pharmacokinetic properties supportive of once-daily dosing. The results from the SILEN-C1 trial (127) suggested that a combination of faldaprevir with Peg-IFN-α+RBV achieved consistently high SVR rates with acceptable tolerability and safety at all dose levels, and all patients with favorable *IL28B* genotypes achieved SVR.

Previous studies have also assessed the the relationship between the favorable *IL28B* genotypes and the SVR of IFN-free regimens in development. The SOUND-C2 study (29) revealed that the week 12 SVR (67-79%) among patients with the *IL28B* CC genotype was higher than that among those without the CC genotype (57-64%). Furthermore, the *IL28B* genotype appears to have a higher predictive value for SVR in patients infected with genotype 1a (CC 75% vs. non-CC 32%) than individuals infected with genotype 1b (CC 82% vs. non-CC 84%) with 28 weeks of treatment. An IFN-free INFORM study (128) of mericitabine as a monotherapy, or in combination with danoprevir, suggested that the *IL28B* genotype may predict viral kinetics. This INFORM study revealed that the rs12979860 CC genotype was associated with faster and earlier viral decline during IFN-free treatment. The mean decrease of HCV RNA level was slightly increased in individuals with the rs12979860 CC genotype compared with those without at the end of IFN-free treatment. These data suggested that the *IL28B* rs12979860 CC genotype appears to be associated with the early viral kinetics of patients receiving IFN-free treatment.

It is likely in the future that combination DAA regimes will be associated with high SVR rates in most populations, and the predictive value of *IL28B* genotyping will become more and more limited. However, DAA therapies, whether IFN-free regimens or PI/Peg-IFN-α+RBV triple therapy, are expensive compared with standard Peg-IFN-α+RBV therapy (129). *IL28B* genotyping will therefore remain clinically useful to determine suitable treatments for individuals and to identify rational and personal treatment approaches.

Other host genetic factors associated with antiviral responses. i) IFN-α pathway genes. Multiple *IFN-α* pathway genes involved in antiviral responses have been identified as candidate functional genes, and studied to determine whether their polymorphisms act as predictive factors for antiviral treatment.

Human MX dynamin like GTPase 1 (MxA) is an IFN-inducible protein that exhibits antiviral activity against a variety of RNA viruses. Hijikata *et al* (130) first reported that the 88 G/T variant within an IFN-stimulated response element-like sequence in the promoter of *MxA* gene may affect the expression of MxA protein, and thus be associated with the IFN-treatment response of patients infected with HCV. These findings have been reproduced by other small independent studies (131-133). IFN-α signaling via interferon α and β receptor subunit IFNAR) 1/2 may be suppressed by the suppressors of cytokine signaling (SOCS) 1/2 heterodimer. Persico *et al* (134) reported an association of a functional *SOCS3* promoter polymorphism (-4874A>G) with SVR in Caucasians. Notably, this study demonstrated that *SOCS3* was significantly upregulated in non-responsible patients, with increased *SOCS3* expression observed in homozygous carriers of the common allele.

Welzel *et al* (135) performed a comprehensive study to analyze the relationship between SVR and 56 variants in 13 genes involved in the IFN-α pathway. In this study, logistic regression was used to analyze the influence of other associated cofactors including HCV genotypes, viral load, fibrosis stage, previous treatment with ribavirin and presence of the hemochromatosis (HFE) H63D variant. This study revealed that SVR was associated with gene variants including *IFNAR1 IVS1-22G, IFNAR2 Ex2-33C*, Janus kinase 1 *IVS22+112T* and adenosine deaminase, RNA specific *Ex9+14A*. For the tyrosine kinase (*TYK2)-2256A* variant, a borderline relationship was present among European American patients and a strong association among African American participants; all 10 patients with SVR who were genotyped for *TYK2-2256* carried the A allele compared with 68 of 120 (57%) non-responders. These data suggested that genetic variants in the IFN-α pathway may affect treatment responses of patients infected with HCV. Su *et al* (136) also studied genetic variants in 5 IFN-α signaling pathway genes (signal transducer and activator of transcription 1 (*STAT1*), *STAT2, IFNAR1, IFNAR2*, interferon regulatory factor 9 (*IRF9*) and 12 IFN-stimulated genes (*MX1, MX2*, 2'-5'-oligoadenylate synthetase 1 (*OAS1*), *OAS2, OAS3*, 2'-5'-oligoadenulate synthetase like (*OASL*), *IRF7*, ISG15 ubiquitin-like modifier 2 (*G1P2*), *G1P3*, interferon induced protein 35, *PKR*, C-X-C motif chemokine 10) in patients of African-American and Caucasian-American descent infected with HCV genotype 1. Associations with SVR were detected for three SNPs in the *OASL* gene, which is induced by interferon signaling and encodes a protein that is involved in RNA degradation (rs1169279; rs3213545, rs2859398). In contrast to the study by Welzel *et al*, no association was observed for the remaining genes.

Chemokine and cytokine genes. Cytokines are crucial for the initiation and specificity of the immune response, and induction

of a T helper cell 1 (Th1) immune response has been associated with a favorable clinical outcome. IL-10 predominantly enhances the Th1 response, and functional promoter variants that confer different IL-10 serum levels have been studied (-1082G>A; -819C>T; -592C>A) (137-139). However, only one group reported a significant association with treatment response when adjusting for covariates (138). IL-12 is another cytokine which may trigger a Th1 response. Mueller *et al* (69) studied a variant in the promoter of *IL-12* which may increase IL-12 production (3'-UTR -1188A>C) and reported an association with the -1188A allele and non-response. However, this association was only significant in a subgroup of individuals infected with genotype 1 HCV and with a high viral load (>800,000 IU/ml). IL-18 is a pleiotropic, proinflammatory cytokine that is secreted by monocytes, macrophages and Kupffer cells (140-142). Haas *et al* (143) studied two promoter polymorphisms (-607C>A, -137G>C) which have been implicated in differences of IL-18 expression due to altered binding of transcription factors (144). In Caucasian patients, the -607A allele was associated with SVR and the -137G allele was associated with the likelihood of non-response. However, the associated risks were only moderately altered and no correction for multiple testing or adjustment for other known risk factors was performed (143). Other cytokine genes have been studied in the context of treatment response but have either been negative *(IL-1A, IL-1B, IL-1RN*) (137) or unconfirmed (*IL-5, IL12B*).

Levels of the pro-inflammatory cytokine TNF-α have also been associated with the response to therapy. However, the results differed among previous studies, leaving the function of *TNF-α* gene variants as predictive factors for therapy response unconfirmed (78,139,145,146). The chemokine C-C motif chemokine ligand 5 (RANTES) binds to the C-C motif chemokine receptor 5 on T cells, thereby triggering a Th1 response. Wasmuth *et al* (147) studied a panel of variants in the *RANTES* gene in patients treated with interferon and demonstrated that *RANTES* haplotypes carrying *3' 222 C* and *Int1.1 C* alleles were more rare in patients with SVR than in non-responders to antiviral therapy. However, sub-group analysis demonstrated that the effect of these *RANTES* haplotypes on treatment response were more apparent in patients infected with HCV genotypes 1 and 4. Since *RANTES* haplotypes carrying *Int1.1 C* are known to downregulate its protein transcriptional activity *in vitro*, the haplotype analysis fits the hypothesis that patients with weak T helper 1 lymphocyte response would not respond to antiviral therapy. *RANTES* variants may contribute to the polygenic interaction between the virus and the host immune system and may help to risk-stratify patients prior to treatment.

IFN-γ. IFN-γ demonstrates antiviral activity against the HCV virus and stimulation of the corresponding receptor may also induce expression of IFN-stimulated genes. A functional promoter variant (-764C>G) has been identified as a predictive factor for treatment response in two independent cohorts of patients with chronic HCV infection (148). The variant located in the proximal *IFN-γ* promoter region was significantly associated with sustained virological response. Furthermore, the association between the -764C>G variant and the treatment response was independently significant, confirmed by the multiple logistic regression with ethnicity, viral genotype and HCV RNA level. Functional studies demonstrated that the -764 G allele has a stronger binding affinity to HSF1 than the C allele and endows >2-fold higher promoter activity. These data suggest that the *IFN-γ*-764C>G variant may be used as a genetic marker to predict the SVR rate of patients infected with HCV.

HLA. Several single studies have reported associations between different *HLA* alleles and SVR. A single study from Egypt (149) demonstrated that *HLA DR2* is an important additional host predictor to the long term treatment response in patients with chronic HCV infection. Another study from Spain (150) demonstrated that *HLA* class I *B44* is associated with a higher rate of SVR in Peg-IFN-α+RBV therapy but not in interferon monotherapy. The results from a Chinese study (151) suggested that the response rates to Peg-IFN-α+RBV in patients with *DRB1*07* were higher than those with *DRB1*04*. However, the populations all of these studies were small and the results have not been replicated thus far.

G protein 3 subunit (GNB3). A functional variant (c.825C>T) of the *GNB3* gene encoding the 3 subunit of heteromeric G proteins has been demonstrated to result in truncated, albeit functionally active, splice variants of *GNB3* with an enhanced signal transduction mediated by the C825T allele. Lindemann *et al* (152) studied the influence of C825T allele status on cellular immune responses and observed that proliferation in patients with the homozygous 825T (TT) genotype was ~2-4 fold higher than that of homozygous C825 allele (CC) carriers. Furthermore, lymphocyte chemotaxis and CD4+ T cell counts of individuals with TT+TC genotypes were significantly enhanced compared with the CC genotype. These results suggested that the allele status of C825T variant is associated with immunocompetence *in vitro* and may be a candidate gene associated with an inadequate immune response. Then, Sarrazin *et al* (153) reported that the *GNB3 825 CC* genotype is associated with the SVR of patients treated with conventional IFN and RBV. Ahlenstiel *et al* (154) confirmed this association in HCV/HIV co-infected patients treated with a Peg-IFN-α+RBV treatment regimen, but failed to confirm the association in HCV mono-infected patients.

Toll like receptor 7 (TLR7). TLR7 is a receptor for single stranded RNA and is involved in the immune response against HCV infection. Thus, it is rational to hypothesize that polymorphisms of the *TLR7* gene are associated with the natural course of chronic HCV infection and the outcome of therapy. Notably, the *TLR7* gene is located on the X chromosome and genetic variation in this gene may explain gender differences. Schott *et al* (155) analyzed *TLR7* polymorphisms and identified the c.32A>T variant as a predictor of non-response in female patients. Their results suggested that this X-chromosomal variation impaired the immune response against HCV infection. However, the study was hampered as it combined different ethnicities and the results failed to be formally reproduced in the subgroup of Caucasian patients.

HFE gene. Lebray *et al* (156) analyzed hepatic histology results in a large cohort of individuals with chronic hepatitis C and

assessed the influence of the *HFE* gene polymorphism on the progression and treatment of chronic hepatitis C. The results demonstrated that iron serum parameters in patients who were heterozygous for the *C282Y* and *H63D* variants were significantly higher than that in those without these mutations. The intrahepatic iron load was higher in subjects with the *H63D* mutation only. No association was observed between *HFE* genetic variants and histological activity. Univariate analysis suggested that only elevated iron parameters were associated with liver disease severity. The data suggested that increased ferritinaemia was a negative predictive factor, whereas the *H63D* variant was a positive predictive factor for IFN-α base treatment responses.

CTLA4. Yee *et al* (157) examined the relationships between *CTLA4* polymorphisms at promoter site -318 and exon-1 site 49 and treatment responses of Peg-IFN-α+RBV therapy. This study demonstrated that virus load declined more rapidly in patients with 49 G alleles or the 318C-49 G haplotype when these patients with HCV genotype 1 infection received Peg-IFN-α+RBV therapy. The data suggested that *CTLA4* 49 G in exon 1 alone and in a haplotype with -318C promoter affects the sustained Peg-IFN-α+RBV therapy response.

Hepatic steatosis and other host predictors. Hepatic steatosis is common in patients with chronic HCV infection. Although the etiology of steatosis in hepatitis C remains to be fully understood, previous independent studies have reported that hepatic steatosis in hepatitis C influenced viral kinetics and was a negative predictive factor of anti-HCV treatment response. Patton *et al* (158) examined liver biopsies from 574 individuals with chronic HCV infection and revealed that non-responders had a greater degree of hepatic steatosis prior to treatment compared with subjects who achieved SVR. This result suggested that hepatic steatosis is significantly associated with the progression of hepatic fibrosis and resulted in the reduced likelihood of achieving a positive treatment response in patients infected with HCV genotype 1. Another previous study (159), including 231 patients with HCV treated with Peg-IFN-α+RBV, also suggested that hepatic steatosis impairs the early reduction of HCV RNA during treatment and had a negative influence on the treatment responses in patients infected with HCV, except those with HCV genotype 3 infection. Previous data also revealed that steatosis was significantly associated with a higher rates of relapse in patients with HCV genotype 3 infection who had a rapid VR (160). Restivo *et al* (161) additionally demonstrated that steatosis was the independent predictive factor of relapse in patients with HCV genotype 3 infection, but not patients infected with HCV genotype 2 treated for 12 weeks with Peg-IFN-α+RBV. Based on these findings, it is rational to infer that taking appropriate interventions aiming at reducing pretreatment hepatic steatosis may be of benefit to patients infected with HCV, apart from those infected with genotype 3.

Other negative predictors of the response to anti-HCV treatment include liver cirrhosis, age ≥40 years, insulin resistance (162,163) and metabolic syndrome (164,165). All of these host prognostic factors predicting the efficacy of anti-HCV therapy are well reviewed elsewhere (166) and thus are not detailed in the present review.

Host genetic factors associated with the side effects of antivirus therapy. RBV-induced haemolytic anemia is one of the most important treatment-limiting adverse effects associated with Peg-IFN-α+RBV therapy. Haemolytic anemia during Peg-IFN-α+RBV treatment is associated with poorer treatment responses, which affects most patients and results in dose modification in ~15% of patients. Fellay *et al* (167) demonstrated that two variants (rs1127354 and rs7270101) in the inosine triphosphatase (*ITPA*) gene, which confers a corresponding enzyme deficiency, are associated with hemoglobin reduction in patients treated with ribavirin. These data were confirmed by the GWAS conducted by Thompson *et al* (168). Inosine triphosphatase (ITPase) deficiency is associated with a reduced need for RBV dose reduction, but has not been associated with SVR (167,169,170). The minor alleles associated with ITPase deficiency protect against RBV-induced haemolytic anaemia. Mechanistically, both polymorphisms have been well characterized and result in ITPase deficiency, allowing accumulation of erythrocyte ITP in red blood cells. The increased levels of ITP in red blood cells associated with ITPase deficiency have been demonstrated to substitute for GTP in the synthesis of ATP, maintaining the erythrocyte ATP pool and preventing oxidative stress (171).

Neuropsychiatric side effects of IFN may additionally limit treatment outcome. Although the GWAS conducted by Thompson *et al* (168) revealed that no common genetic variants were associated with IFN-induced neutropenia or leucopenia. A retrospective investigation from Gochee *et al* (172) studied apolipoprotein E (*APOE*) genotypes which have been identified as associated with Alzheimer's disease (173). This retrospective investigation suggested that there was an association between APOE genotypes and IFN-α-induced neuropsychiatric complications. individuals carrying an ε4 allele were more likely to exhibit neuropsychiatric symptoms during Peg-IFN-α+RBV therapy than those without an ε4 allele. The results indicated that the *APOE* genotype may affect the risk of neuropsychiatric symptoms for patients receiving Peg-IFN-α+RBV therapy. However, the pathophysiology behind this association is not clear and requires further study. Furthermore, this study was a retrospective investigation; thus, more prospective studies are required to assess the association between *APOE* genotype and susceptibility to neuropsychiatric side effects of IFN-treatment.

Leucocytopenia and thrombocytopenia are other common side effects of treatment. Leucocytopenia has been reported to be associated with variants in the *INFAR1* (c.10848A>G) and *STAT2* (c.4747G>T) genes. Thrombocytopenia is associated with a variant in the *IRF7* gene (c.789G>A). However, this association was no longer significant upon adjustment for confounding factors (174).

Host factors associated with fibrosis progression. The occurrence of liver fibrosis and the pace of progression to liver cirrhosis is highly variable among different patients and ranges from <10 years to several decades (175,176). Epidemiological studies have reported that the rate of fibrosis progression is accelerated among older males with higher alcohol consumption, HIV co-infection, insulin resistance and elevated body mass index (177,178). However, multivariable analysis suggests that these factors contribute to <30% of variation in fibrosis progression (179). Therefore, it has been hypothesized that

multiple host genetic factors may account for the variable rates of fibrosis progression.

In the last decade, a number of possible genetic variants in genes associated the progression of liver fibrosis were identified by candidate gene association studies. These genetic factors may explain the variable occurrence of liver fibrosis and the pace of progression to liver cirrhosis in individuals infected with the same etiological agent. However, most of the studies used small cohorts and failed to be replicated. For example, contradictory results have been obtained in studies that evaluated the influence of variants in the hemochromatosis gene on fibrosis progression in individuals with chronic HCV infection (180). Huang *et al* (181) performed a large-scale, well-designed genetic disease association study with 24,832 putative functional variants and demonstrated that 7 genetic variants were significantly associated with a rapid rate of fibrosis progression in chronic HCV infection. The genes included are antizyme inhibitor 1, transient receptor potential cation channel subfamily M member 5, toll-like receptor 4, aquaporin 2, *rs17740066, rs2290351*, and *rs4290029*. Previous investigations assessed the value of the cirrhosis risk score (CRS) based on these associated SNPs for the early prediction of fibrosis progression in patients with CHC with mild liver fibrosis, and validated host genetics defined by CRS predict fibrosis progression in males with initially mild chronic hepatitis C and may become a useful parameter for prognostic evaluation and treatment decision in several independent cohorts including small numbers of patients with or without fibrosis progression (182,183). However, prior to recommending CRS as a clinical tool, large prospective cohorts are required to further validate the predicted value of CRS.

Previous GWAS have additionally been used to analyze host genetic variations involved in fibrosis progression. Thompson *et al* (184) investigated the influence of *IL28B* polymorphisms on the progression of liver fibrosis. Their GWAS suggested that there was a significant association between the favorable *IL28B* genotype and increased levels of alanine transaminase and a more active inflammatory grade on biopsy, but the potential association between the *IL28B* genotype and fibrosis progression was not confirmed by this study. The polymorphism (rs738409 C>G) in the patatin-like phospholipase-3 (*PNPLA3*) gene has been identified and demonstrated to affect liver fibrosis progression and steatosis in GWASs including individuals with non-alcoholic fatty liver disease (185). Trepo *et al* (186) evaluated the influence of the *PNPLA3* rs738409 C>G variant on fibrosis progression and steasosis among individuals with chronic HCV infection, and revealed that patients with the G allele of this mutant had an increased chance of steatosis and fibrosis following adjustment for co-factors including age, sex, body mass index, alcohol consumption and diabetes. Numerous other studies have confirmed that *PNPLA3* polymorphism is associated with the susceptibility of fibrosis in individuals with chronic HCV infection (187,188), but other studies failed to confirm this association (189). Further studies are required to assess the predictive value of the *PNPLA3* polymorphism.

Patin *et al* (190) performed a 2-stage genome wide study using 1,161 well-characterized patients infected with HCV who experienced liver biopsies prior to treatment and revealed that two polymorphisms (rs16851720 and rs4374383) were significantly associated with fibrosis progression. The rs16851720 variant is located at the ring finger protein 7 gene, which encodes an important antioxidant involved in apoptosis, while the rs4374383 variant was linked to the MER proto-oncogene, tyrosine kinase and tubby like protein 1 genes, which encode proteins involved in phagocytosis of apoptotic cells by macrophages. However, mechanistic data are not yet available.

4. Summary

In conclusion, both viral and host-related factors influence the natural course and antiviral efficacy of patients with HCV infection. HCV genotype is the most important viral factor predicting the response to Peg-IFN-α+RBV therapy. The subtype of HCV genotype 1 is the key viral factor in predicting the efficacy of DAA treatment. HCV genome heterogeneity and baseline viral load are additionally associated with the treatment response. Multiple host genetic variants localized in certain genes involved in immune response have been identified to be predictors of spontaneous course and therapeutic outcome in chronic hepatitis C. However, the findings from candidate gene association studies have not been proven universal for all investigated populations and independent studies. Previous findings in independent large GWAS confirmed that *IL28B* gene polymorphisms are the key host genetic factors that predict spontaneous HCV clearance and Peg-IFN-α+RBV treatment responsiveness. A genetic variant in the *ITPA* gene has additionally been identified as a protective factor against RBV-induced anemia and dose reductions. The rs738409 C>G *PNPLA3* polymorphism is significantly associated with hepatic steatosis and fibrosis in patients with HCV infection. These findings highlight the importance of further in-depth analysis in the field of pharmacogenomics to improve current therapy standards.

Although certain viral and host factors associated with outcome of patients with HCV infection have not been confirmed by all research and are far from entering clinical practice, these biomarkers not only provide an enhanced understanding of the pathophysiology of chronic HCV infection, but may additionally provide novel ideas in personalized prevention and individualized clinical management of HCV. As therapy using Peg-IFN-α+RBV remains the principal treatment for patients with HCV in developing countries, including China, viral and host genetic factors will still have clinical significance on HCV management for developing countries. Although host and viral markers would appear to be less relevant to HCV management in the era of DAA therapy, a considerable percentage of patients with HCV infection do not respond to DAA therapy due to drug resistance, poor tolerability and the high pill burden. Therefore, efficient and reliable host and viral predictors are required to assess 'ease-to-cure' characteristics, create individual antiviral solutions, improve the efficacy of treatment, shorten therapy duration, reduce side effects and decrease the cost of treatment.

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