Host factors determining the efficacy of hepatitis C treatment

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Abstract  Combination therapy with pegylated interferon and ribavirin is the standard of care (SOC) for the treatment of chronic hepatitis C (CHC). Treating CHC with SOC may show a sustained virological response (SVR) in approximately 50–70 % of genotype 1 CHC patients and an SVR in 70–90 % of genotype 2 CHC patients. The genotype, baseline viral load, and viral kinetics (i.e., rapid virologic response and early virologic response) can be used as predictors of response-guided therapy. Nonetheless, host factors, e.g. age, ethnicity, insulin resistance, and genetic variations, may also play important roles in the SVR in CHC patients treated with SOC. Recent genome-wide association studies have demonstrated that single-nucleotide polymorphisms near the interleukin 28B gene (IL28B) were associated with SVR to treatment with SOC in CHC patients. The IL28B polymorphisms may contribute to the viral kinetics during treatment. Asian people have favorable IL28B polymorphisms. This factor may at least partly explain the high eradication rate of hepatitis C by SOC in Asia. Combination therapy with direct-acting antivirals (DAAs) and SOC can increase the SVR rates both in treatment-naïve and treatment-experienced patients. Although the IL28B polymorphisms also affect the SVR of triple therapy with SOC and first-generation protease inhibitors, pilot studies have demonstrated that potent DAAs might overcome the influence of IL28B polymorphisms. Thus, the treatment of hepatitis C virus infection could be simplified in the near future.

Keywords  Chronic hepatitis C · Hepatitis C virus · IL28B · Pegylated interferon · Sustained virologic response

Introduction

Hepatitis C virus (HCV) infection is one of the most important health issues throughout the world. The estimated worldwide prevalence of HCV infection is around 1–3 %. However, such crude estimates might mask significant differences in prevalence rates among countries, and even in different parts of the same country. According to data reported by the World Health Organization, worldwide, approximately 130–170 million people are infected with hepatitis C, 3–4 million persons are newly infected each year, and more than 350,000 people die from hepatitis C-related liver diseases each year. Of patients acutely infected with HCV, 50–80 % of them will eventually have chronic hepatitis. Once the chronic status is established, the disease progresses gradually. In approximately 10–20 % of patients with chronic hepatitis C (CHC), the disease will lead to liver cirrhosis in 20 years. After the development of liver cirrhosis, the annual rates of hepatocellular carcinoma occurrence are about 1–8 %. Excessive alcohol intake and concurrent HIV infection will accelerate the disease progression [1–8]. Therefore, the
goals of treatment for hepatitis C are to decrease its infectivity, to decrease the risk of cirrhosis or decompensation, to decrease the development of hepatocellular carcinoma, and to improve the survival and quality of life of the patients [1–14].

Standard of care and response-guided therapy

Interferon (IFN)-α was the therapeutic agent first approved for chronic HCV infection, in the 1980s. With IFN monotherapy, a sustained virologic response (SVR) could be achieved in 6–20 % of patients with CHC in Western countries [15–18]. However, the SVR rates were much higher in Asian studies [4, 11–14, 19–22]. Higher doses of IFN and longer durations of treatment may result in higher SVR rates. The HCV genotype, HCV viral load, and pre-existent cirrhosis are important predictors of SVR in CHC patients receiving IFN monotherapy [4, 11–22].

A pilot study by Lai et al. [23] demonstrated that the addition of ribavirin in the treatment of CHC could significantly increase the SVR rates. With conventional IFN and ribavirin treatment, large-scale studies in Western countries demonstrated that the SVR rates of a 24-week regimen and a 48-week regimen in genotype 1 CHC patients were 30–35 % and around 40 %, respectively [17, 18]. Again, the results from clinical trials in Taiwan revealed higher SVR rates for combination therapy with conventional IFN and ribavirin for only 24 weeks [22–25].

The addition of polyethylene glycol molecules to IFNs (pegylation, forming pegylated [peg] IFNs) changes some IFN characteristics, such that pegIFNs, compared with conventional IFNs, show prolonged half-life in plasma, reduced clearance, and decreased immunogenicity. Hence, pegylated IFNs have a longer half-life and better efficacy than IFNs. Combination therapy with pegIFN and ribavirin achieved higher SVR rates than combination therapy with conventional IFN and ribavirin [26–28]. Therefore, combination therapy with pegIFN and ribavirin has become the standard of care (SOC) for CHC, especially in most Asian countries. The SVR rates with 48-week pegIFN and ribavirin combination therapy in genotype 1 CHC were around 50 % in Western countries [26–30]. The SVR rates with 24-week pegIFN and ribavirin combination therapy in genotype 2 CHC were higher than 80 % in Western countries [28, 29, 31–33]. Surprisingly, studies in Asia showed SVR rates of 70–80 % in genotype 1 CHC patients treated with pegIFN and ribavirin for 48 weeks, and SVR rates of 90–95 % in genotype 2 CHC treated for 24 weeks [4, 34–38].

About 40 % of genotype 1 CHC patients achieved a rapid virologic response (RVR) by SOC. The SVR rate was 90 % in patients with RVR who received the combination therapy for only 24 weeks [36–38]. In genotype 1 CHC patients with an RVR and low viral load, the SVR rate of the 24-week regimen was as good as that of the 48-week regimen. The SVR rates were 96 and 100 %, respectively [37]. Approximately 90 % of the genotype 2 CHC patients reached an RVR. In patients with an RVR, the SVR rates in a 16-week group and a 24-week group were 100 and 98 %, respectively [35]. The lack of an early virologic response (EVR) in genotype 1 CHC is a critical predictor of a non-responder [27, 37], with a negative predictive value of 100 % [37]. Against this background, a roadmap for individualized HCV therapy in Asian people is suggested, as follows. For genotype 1 CHC, the optimal treatment duration is 48 weeks, but a 24-week regimen may be sufficient for patients with an RVR and low viral load. For genotype 2 CHC, the treatment duration is 24 weeks. However, a short-term treatment with pegIFN and ribavirin is effective for patients with an RVR. For patients without an EVR, stopping the treatment is suggested because of the poor response by SOC [4]. These suggestions are similar to the recommendations made by the Asian Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Diseases (AASLD), and the European Association for the Study of the Liver (EASL) [4, 5, 7, 8].

Host factors determining the efficacy of hepatitis C treatment

Besides the baseline virological factors, on-treatment viral kinetics, and antiviral agents, host factors such as age, insulin resistance, ethnicity, and genetic variations, may also play important roles in the achievement of an SVR in CHC.

The efficacy and safety of treating elderly CHC patients are still controversial issues. It has been suggested that elderly patients chronically infected with HCV might suffer from more adverse effects on IFN-based therapy and have higher rates of drug modification or discontinuation. Thus, the elderly could have lower SVR rates to IFN-based therapy [39–42]. However, various results have been shown [43, 44]. In a prospective study by Huang et al. [44], it was found that the treatment response was substantially lower in elderly patients than in patients between the ages of 50 and 64 years, especially in patients infected with genotype 1 HCV. Also, the elderly patients, who received 48 weeks of treatment, had significantly higher rates of grade 3 or 4 adverse side effects, dose modification, and discontinuation. However, the per-protocol analysis revealed that the elderly patients had an SVR rate similar to that of the younger patients. In addition, elderly patients...
with an RVR showed high SVR rates that were comparable to rates in the younger patients [44]. Thus, an individualized therapy is more suitable for elderly patients. Shortening the treatment duration and reducing the drug-related adverse events might enhance the treatment adherence of the elderly and lead to a better response to the treatment for CHC [45].

Since the introduction of IFN-\(\alpha\) for the treatment of CHC, it was found that SVR rates were much higher in Asian people [4, 11–14, 19–22] than those reported in Western studies [15–18]. The addition of ribavirin in the treatment of CHC significantly increased the SVR rates and decreased the relapse rates [23]. Large-scale studies in Western countries demonstrated that the SVR rates with conventional IFN and ribavirin treatment in genotype 1 CHC patients were around 30–40 % [17, 18]. However, the SVR results in those studies were far less than the SVR rates in Asian trials [22–25]. The pegIFN and ribavirin combination therapy (SOC) might achieve higher SVR rates than the combination therapy with conventional IFN and ribavirin [26–28]. The SVR rates of pegIFN and ribavirin combination therapy in genotype 1 and genotype 2 CHC in Western countries were around 50 and 80 %, respectively [26–33]. However, the Asian studies showed SVR rates of 70–80 % in genotype 1 CHC patients and 90–95 % in genotype 2 CHC [4, 34–38]. Furthermore, the SVR rates to SOC in African Americans with chronic HCV infection were also lower than those in Hispanic and Caucasian Americans [46, 47]. These results implied that ethnicity is a very important factor influencing the treatment outcome of SOC to CHC [4].

There is an association between chronic HCV infection and metabolic diseases, e.g., insulin resistance and lipid synthesis disturbances [48, 49]. Several studies have postulated a strong association between chronic HCV infection and increased prevalences of insulin resistance [50–52] and type 2 diabetes mellitus [53–55]. The presence of insulin resistance and diabetes mellitus might impair the response to pegIFN and ribavirin combination therapy, and lead to a lower SVR rate [56–58]. Interestingly, sustained suppression or clearance of HCV appeared to attenuate insulin resistance, restore beta-cell function, and reduce glucose abnormalities [59–64]. These findings strongly suggested a causal relationship between chronic HCV infection and insulin resistance.

CHC patients might have higher prevalences of various immunological phenomena, including positivity for autoantibodies [65]. Antinuclear antibody (ANA), a marker of autoimmune liver disease and other inflammatory conditions, is often detected in patients with chronic HCV infection [66]. ANA seropositivity has been found to be correlated with lower HCV RNA levels, old age, and advanced fibrosis in CHC patients [67]. The response to IFN or IFN and ribavirin combination therapy in ANA-positive CHC patients was controversial [68–70]. No differences between autoantibody-positive and autoantibody-negative patients in responses to IFN-based treatment have been reported [68, 69]. But it has been found that there is a tendency towards worse long-term responses in autoantibody-positive patients [70]. A recent article demonstrated that a high ANA titer (>1:80) was an independent factor associated with SVR to pegIFN and ribavirin combination therapy in HCV non-1 genotype patients [71]. However, the frequencies of adverse events with pegIFN and ribavirin combination therapy were not increased in these ANA-positive patients [71].

Tumor necrosis factor (TNF)-\(\alpha\) is a pro-inflammatory cytokine. It is an important pathogenic mediator in liver diseases. TNF-\(\alpha\) may be involved in the pathogenesis of acute and chronic HCV infection, the persistence of the virus, and the response to IFN therapy [72]. Some genetic polymorphisms in the human TNF-\(\alpha\) promoter region, such as the G-to-A transition at positions −308 and −238, have been shown to influence TNF-\(\alpha\) expression. At position −308, allele 2 (A; TNF308.2) is associated with higher constitutive and inducible levels of TNF-\(\alpha\) than is allele 1 (G; TNF308.1) [73]. At position −238, allele 2 (A; TNF238.2) has been reported to be associated with certain autoimmune and infectious diseases [74]. Although conflicting data on the associations between TNF-\(\alpha\) promoter polymorphisms and the pathogenesis and progression of chronic HCV infection, and the response to IFN-\(\alpha\) therapy, have been reported [75], the TNF-\(\alpha\) promoter polymorphism at position −308 may be helpful to predict the response to combination therapy in genotype 1 CHC patients, especially in genotype 1 CHC patients with a high viral load [76].

Human leukocyte antigens (HLAs), encoded by the major histocompatibility complexes, play an important role in the host responses to infection [77, 78]. HLA class I and class II molecules are pivotal to the host immune response via presenting antigen to CD8+ cytotoxic T cells and CD4+ helper T cells. Specific HLA alleles have been reported to be related to the persistence or spontaneous clearance of HCV, HCV viral load, progression of liver fibrosis, and the antiviral response to conventional IFN monotherapy [79–83]. HLA class I antigen was also shown to be associated with an SVR to IFN and ribavirin combination therapy in patients with CHC [84]. However, only a few reports have studied the association between HLA alleles and response to pegIFN and ribavirin combination therapy [85]. A study conducted in Taiwan, aiming to elucidate the association between HLA loci and responses to pegIFN and ribavirin therapy, postulated that the HLA A24 and B40 alleles were significantly associated with SVR after adjustment for confounding factors including...
HCV genotype, hepatic fibrosis, and pretreatment serum HCV RNA levels [85]. Regarding the HLA haplotypes, B40-DRB1*3, B46-DRB1*9, Cw1-DQB1*3, and Cw1-DRB1*9 were significantly associated with an SVR to combination therapy [85]. These results suggested that host immunogenetic factors may be used to predict the response to combination therapy in CHC patients.

Genome-wide association studies (GWAS) of samples from the IDEAL trial and another prospective treatment study demonstrated that a host single-nucleotide polymorphism (SNP) near the interleukin 28B (IL28B) gene (interferon lambda 3 gene) was strongly associated with SVR to treatment with pegIFN and ribavirin in CHC patients in all ethnic groups [86]. A Duke University group also found that SNP rs12979860 C-allele frequencies were different in diverse ethnic groups. The study by Ge et al. [86] showed that the distribution of the IL28B polymorphism may, at least partly, explain the different SVR rates to the same treatment regimen for CHC in different ethnicities [86]. A GWAS study of SVR to pegIFN and ribavirin combination therapy in Australian patients with genotype 1 CHC [87] presented a result similar to that of the study by Ge et al. [86]. An association between IL28B polymorphism and response to pegIFN and ribavirin combination therapy was also reported by Tanaka et al. [88] in Japanese patients with genotype 1 CHC. The IL28B polymorphism was also significantly correlated with spontaneous HCV clearance in patients with acute HCV infection. Patients with the rs8099917 TT genotype had a higher rate of spontaneous HCV clearance [89].

Liu et al. [90] postulated that RVR, IL28B polymorphism, treatment duration, and low viral load were independent factors for SVR in Taiwanese patients with genotype 1 chronic HCV infection treated with pegIFN and ribavirin. Many studies showed that the IL28B polymorphism was strongly associated with RVR and SVR to the treatment with SOC in genotype 1 CHC [86–88, 90–93]. However, further analysis demonstrated that the differences in SVR rates were not significant among RVR patients with different IL28B genotypes. Only in patients without an RVR, the IL28B polymorphism may influence the SVR to pegIFN and ribavirin combination therapy [91–93]. For genotype 1 CHC patients without an RVR, the complete early virologic response (cEVR) is an important predictor of SVR in patients treated with pegIFN and ribavirin for 48 weeks [94]. It was found that the IL28B polymorphism was an independent factor for SVR in genotype 1 CHC patients without an RVR [91–93]. However, when cEVR was included in a multivariate analysis, the role of the IL28B polymorphism was not significant [93]. Therefore, the on-treatment viral kinetics is more important than the IL28B polymorphism in determining the response to pegIFN and ribavirin combination therapy in CHC patients. The role of the IL28B polymorphism was not so important in the treatment with SOC in genotype 2 and 3 CHC patients. The differences in SVR rates were not statistically significant among different IL28B genotypes in genotype 2 and 3 CHC patients [95–97]. An association of the SNP rs72258881 polymorphism [a (TA) di-nucleotide repeat located in the promoter region of IL28B] and IL28B gene expression was postulated by Sugiyama et al. [98]. This genetic variation of the IL28B promoter may affect the gene expression in a (TA)₉ length-dependent manner. However, the significance of this polymorphism needs further clinical validation.

**Combined host and viral factors for personalized genotype 1 HCV therapy**

According to the suggestions in various guidelines [5, 7, 8], a 24-week regimen may be sufficient for genotype 1 CHC patients with an RVR and low viral load [5, 7, 8]. The SVR rates were higher than 90 % in genotype 1 CHC patients with an RVR and low viral load when treated with pegIFN and ribavirin for 24 weeks [37, 38, 99–101]. However, only 20–40 % of genotype 1 CHC patients met these criteria. Is it possible to identify HCV genotype 1 superresponders before starting antiviral therapy? The answer is yes. IL28B genotype combined with baseline viral load may help in identifying HCV genotype 1 patients who will or will not benefit from a 24-week regimen before starting the therapy. The positive predictive value of these two factors was 80 % and the negative predictive value was 91 % [92].

According to the suggestions in the guidelines [5, 7, 8], for genotype 1 CHC patients only with a partial early virologic response (pEVR), the suggested duration for pegIFN and ribavirin therapy was 72 weeks [5, 7, 8]. Can we more precisely identify HCV genotype 1 patients who will benefit from the 72-week regimen? For genotype 1 CHC patients only with a pEVR, the 72-week-regimen group had a lower relapse rate than the 48-week-regimen group in patients carrying the IL28B rs12979860 non-CC genotype [102]. So HCV-1 slow responders carrying the IL28B rs12979860 non-CC genotype may benefit from extended therapy to 72 weeks.

According to the suggestions in the guidelines [5, 7, 8], the treatment in genotype 1 CHC patients should be stopped if the patients have no EVR (less than 2 log₁₀ IU/mL viral reduction at treatment week 12) or if the serum HCV RNA is still positive at week 24 of the treatment [5, 7, 8]. Could this result be applicable to identify HCV genotype 1 patients who will not respond to 48 weeks of SOC before week 12 of treatment? A combination of week 4 IFN-responsiveness and IL28B genotype was used for
predicting treatment failure [103]; the negative predictive value for HCV RNA >10,000 IU/mL at week 4 of treatment and non-TT genotype was 94 %. And the negative predictive value for an HCV RNA reduction of less than 1 log_{10} IU/mL at week 4 of treatment was 92 %. With a strategy of sequential stopping rules, 53.7 % (73/136) of non-responders were identified (43.4 % at week 4, and 10.3 % more at week 12). As compared with a non-responder detection rate of 40.4 % (using the classical 12-week stopping rule), the new sequential stopping rules could detect more non-responders and could enable the earlier stopping of the treatment [103].

**The role of host factors in the DAA era**

There are many direct-acting antiviral agents (DAAs) under investigation, including protease inhibitors, RNA polymerase inhibitors, and non-structure protein (NS) 5A inhibitors [104, 105]. To date, only 2 first-generation protease inhibitors have been approved in the United States and Europe. They are telaprevir and boceprevir [106–109]. Overall, triple therapy with the first-generation protease inhibitors and SOC can increase SVR rates from 40 to 70 % in treatment-naive patients, and from 20 to 65 % in treatment-experienced patients with genotype 1 CHC [106–109]. Telaprevir has been approved in Japan. The SVR rates in genotype 1 Japanese CHC patients treated with telaprevir-based therapy for 24 weeks were around 70 %, even in treatment-experienced patients [110–112]. Nonetheless, the IL28B polymorphisms also affect the SVR of triple therapy with SOC and first-generation protease inhibitors. In treatment-naive genotype 1 CHC patients receiving triple therapy, the patients with the IL28B CC genotype had higher SVR rates [106, 107]. The same trend was also observed in treatment-experienced genotype 1 CHC patients [108, 109].

Although the triple therapy with first-generation DAAs and current SOC may increase SVR rates, the triple therapy can enhance adverse events, such as anemia, skin rash, and gastro-intestinal symptoms [106–109]. In addition, the complexity of the treatment might influence adherence to treatment, as has been shown in HIV-infected patients receiving highly active antiretroviral therapy. CHC patients receiving the triple therapy could be taking as many as 18 tablets per day for this antiviral therapy. Therefore, the triple therapy may be limited to genotype 1 and genotype 4 treatment-naive CHC patients with a poor IL28B genotype or without an RVR, and to genotype 1 and genotype 4 previous non-responders, especially in regions such as Asia where people have a favorable IL28B genotype. For patients with genotype 2 and genotype 3 HCV, and genotype 1 and genotype 4 patients with a good IL28B genotype and/or RVR, the dual therapy with pegIFN and ribavirin may be sufficient, unless ultra-short triple therapy is proven to be effective.

A pilot study conducted by Chayama et al. demonstrated that potent DAAs might overcome the influence of IL28B polymorphisms in Japanese CHC patients [113]. An NS5A inhibitor (daclatasvir) and an NS3 protease inhibitor (asunaprevir) were used for genotype 1 CHC null responders. The results were quite exciting. Nine out of the 10 genotype 1b patients had achieved an SVR at week 24 after the end of treatment. The patient who discontinued the treatment at week 2 also showed negativity for serum HCV RNA at week 24 of follow up. Lok et al. [114] reported that the combination of an NS5A inhibitor and an NS3 protease inhibitor with SOC was effective for American genotype 1 CHC null responders. The SVR rate was 90 %. Although the SVR rate for the IFN and ribavirin-free regimen was only 36 %, both of the patients with genotype 1b HCV obtained an SVR [114]. Gane et al. further demonstrated that combination therapy with an NS5B RNA polymerase inhibitor and ribavirin for 12 weeks achieved an SVR of 100 % in treatment-naive genotype 2 and 3 CHC patients [115]. The major genotypes of HCV in East Asia are genotypes 1b, 2, and 3. Therefore, we believe that the eradication of HCV with an IFN and ribavirin-free regimen will come true in the near future in East Asia.

**Summary**

In summary, combination therapy of pegIFN and ribavirin is still the SOC for the treatment of CHC in most Asian countries. As well as baseline virological factors, on-treatment viral kinetics, and antiviral agents, host factors may also play important roles in SVR. The IL28B polymorphism is strongly associated with the response to SOC in genotype 1 CHC. The IL28B genotype combined with baseline viral load and on-treatment viral response may help in identifying genotype 1 CHC patients who will or will not benefit from a 24-week regimen, as well as helping to identify the HCV genotype 1 slow responders who will benefit from extended therapy to 72 weeks, and predicting the genotype 1 CHC patients who will encounter a treatment failure with the SOC. Combination therapy with DAA and SOC can increase the SVR rates in both treatment-naive patients and treatment-experienced patients. In treatment-naive and treatment-experienced genotype 1 CHC patients receiving triple therapy the patients with an IL28B favorable genotype still had higher SVR rates. Pilot studies have demonstrated that potent DAAs might overcome the influence of IL28B polymorphisms. Nonetheless, the role of DAA treatment in Asian CHC patients needs further investigation.
Conflict of interest  The authors declare that they have no conflicts of interest.

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