Tailor-Made Therapy for Viral Hepatitis: Recent Advances

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Key Words

Hepatitis C • Hepatitis B • Interleukin-28B • Inosine triphosphatase • Pegylated interferon ribavirin therapy • Double-filtration plasmapheresis

Abstract

Combination therapy of pegylated interferon- α with ribavirin (PEG-IFN/RBV) is a standard of care for chronic hepatitis C (CHC). The majority of CHC patients are infected with HCV genotype I. The recent discovery revealed by a genome-wide association study technology provides the important role of interleukin-28B (IL28B) and inosine triphosphatase (ITPA) in HCV infection. In addition, response to PEG-IFN/RBV therapy is correlated with insulin resistance, hepatic steatosis, and hepatic fibrosis in CHC patients. Double-filtration plasmapheresis together with IFN therapy has proved to be effective in the reduction of viral load during the early stage of treatment. In CHC patients, not only IL28B status, but also the treatment period of PEG-IFN/RBV is important. Even when new polymerase/protease inhibitors are introduced in the treatment of CHC, tailor-made treatment for CHC using IL28B, inosine triphosphatase testing or double-filtration plasmapheresis treatment prolonged treatment strategy is highly recommended. The relative etiologic role of prior hepatitis B virus infection in the development of non-B non-C hepatocellular carcinoma is also known in hepatitis B-endemic areas.

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Introduction

The 8th Japan-Korea Liver Symposium, the main theme of which was ‘Tailor-made therapy of viral hepatitis’, was held in Kobe, Japan, on July 17, 2011, to focus on and discuss current topics in viral hepatitis. The symposium was full of enlightening lectures by world’s leading scientists, followed by extensive discussions. This supplement issue of *Digestion* contains the most important articles presented at this meeting.

Insulin Resistance

Insulin resistance (IR) has been reported to be an independent predictor of treatment outcome in chronic hepatitis C (CHC) patients.

Associations among IR, steatosis and liver fibrosis have been observed in CHC patients [1–5]. IR has been suggested as the cause, more than a consequence, of hepatic steatosis and fibrosis in patients with HCV, particularly in those with genotype 1 infection [6]. The mechanisms of the more obvious and crucial influence of IR, more than steatosis and fibrosis, need further study. IR seems to be at least associated with body mass index and steatosis, but not with hepatic fibrosis [7].

Double-Filtration Plasmapheresis

The use of double-filtration plasmapheresis (DFPP), approved in Japan in April 2008 for the retreatment of chronic CHC patients with genotype 1b and high viral loads, together with IFN administration has produced a substantial reduction in the viral load during the early stages of treatment and has effected a high sustained virological response (SVR) [8, 9], suggesting that this treatment is a new modality for difficult-to-treat CHC patients.

Recent reports have revealed factors associated with response to pegylated interferon- α with ribavirin (PEG-IFN/RBV) therapy such as single nucleotide polymorphisms (SNPs), as host genetic factors, located in interleukin-28B (IL28B; rs8105790, rs11881222, rs8103142, rs28416813, rs4803219, rs8099917, rs7248668, and rs12979860) on chromosome 19 [10–13]; amino acid (aa) substitutions in nonstructural protein 5a, especially those in the IFN/RBV resistance-determining region [14] and the IFN sensitivity-determining region (ISDR) [15], and the core regions of HCV [16], as viral genetic polymorphisms.

Kim et al. [17] reported that early viral dynamics with DFPP + IFN- β /RBV then PEG-IFN/RBV therapy is superior to the previous PEG-IFN/RBV combination therapy. There was a significant difference in viral reduction at 24 and 48 h, and 1, 2, 4, 8 and 12 weeks between non-viral response (NVR) and relapse patients. The rate of rapid viral response (RVR) and complete early viral response (cEVR) showed a significant difference between NVR and relapse patients: among the 20 patients, RVR was obtained in 75% (6/8) of relapse patients but in 0% (0/12) of NVR patients, and cEVR in 88% (7/8) of relapse patients but in only 8% (1/12) of NVR patients. On the basis of the above results, DFPP + IFN- β /RBV then PEG-IFN/RBV therapy is indicated more for relapse than for NVR patients. We could conclude that relapse patients would be better candidates than NVR patients [17].

IL28B and Inosine Triphosphatase

The recent discovery revealed by a genome-wide association study (GWAS) technology provides the unexpected role of *IL28B* and inosine triphosphatase (*ITPA*) in HCV infection. The former SNPs around the *IL28B* gene could improve the diagnostics on the prediction of spontaneous clearance and the response to anti-HCV treatment, suggesting that these findings could be strong evidence to enhance the development of a novel therapeutic

strategy and the basic study of IFN- λ s. Interestingly, the discovered *IL28B* SNPs revealed the enigma that the viral clearance rate was dependent on ethnic type. The latter functional SNP in *ITPA* locus was the most significant SNP associated with RBV-induced anemia as well as IFN-induced thrombocytopenia. Note that severe Hb decline, which is mainly found in *ITPA*-CC patients, was inversely correlated with platelet reduction, contributing to an association between severe anemia and relative reactive increase in platelet count.

The efficacy of triple therapy of telaprevir/PEG-IFN/RBV was high in the patients with genotype TT (rs8099917), who achieved SVR (84%), irrespective of substitution of core aa70. In the patients having genotype non-TT, those of Arg70 gained high SVR rate (50%), and SVR rate (12%) was the worst in patients who possessed both genotype non-TT and Gln70 (His70), suggesting genetic variation near the *IL28B* gene and aa substitution of the core region as predictors of SVR to a triple therapy in Japanese patients infected with HCV genotype 1b [18].

Genetic variants leading to *ITPA* deficiency, a condition not thought to be clinically important, protect against hemolytic anemia in CHC patients receiving RBV [19]. Results obtained in one GWAS study need to be evaluated in the context of different geographical and racial populations and independent cohorts. Tanaka confirmed that *ITPA* SNP (rs1127354) was a useful predictor of RBV-induced anemia in Japanese patients [20]. Excluding those with genotype 1b and high viral load, patients with *ITPA* minor variant A achieved significantly higher SVR rates than those with the major variant (CC; 96 vs. 70%, respectively, $p = 0.0066$) [20]. Because the typical PEG-IFN/RBV treatment period is shorter (24 weeks) in genotype 1 low viral load and genotype 2 patients than in genotype 1 high viral load (48 weeks) patients, early dose reduction in RBV may be more critical for the final outcome.

The recent discovery revealed by GWAS technology provides the unexpected role of *IL28B* and *ITPA* in HCV infection. These data may provide a valuable pharmacogenetic diagnostic tool for tailoring PEG-IFN/RBV dosing to minimize drug-induced adverse events and for further optimization of clinical anti-HCV chemotherapeutics.

Total PEG-IFN Dose, Core 70 Substitution and ISDR Substitution

Takita et al. [21] showed in their multivariate analysis that rs8099917 genotype and total PEG-IFN dose contribute to the successful outcome of PEG-IFN plus riba-

virin combination treatment for infection with HCV genotype 1. The study indicated the value of a combination of the rs8099917 genotype and core 70 substitutions for prediction of SVR. The patients with the rs8099917 genotype TT had high rates of SVR (67.9%). SVR was achieved by 30.7% of patients with the rs8099917 genotype non-TT and core 70 wild type. The SVR rate was worst in patients with rs8099917 genotype non-TT and core 70 mutant type. These results indicate the effects of both host and viral factors on IFN responsiveness. However, a combination of the IL28 genotype and ISDR substitutions for prediction of SVR was not useful.

Etiologic Role of Prior Hepatitis B Infection and Nonalcoholic Steatohepatitis on Hepatocellular Carcinoma Occurrence

A previous study on 1,145 Korean patients showed that the prevalence of cryptogenic hepatocellular carcinoma (HCC) was significantly increased during the last decade, and patients with cryptogenic HCC had a tendency to have risk factors for nonalcoholic fatty liver disease (NAFLD) such as DM, hypertension and obesity than those with virus or alcohol-related HCC [22]. It can be assumed that the increased proportion of risk factors for NAFLD may contribute to the development of cryptogenic HCC. However, there has been no study to compare the relative etiological role of prior HBV infection and NAFLD in the development of NBNC-HCC in HBV-endemic areas. Cho et al. [23] show in their study that the relative proportion of NAFLD-related HCC increased more than three times during the past 10 years, while that of prior HBV infection-related HCC decreased. A growing trend towards a rise in NAFLD-related HCC is expected in the near future, while the prevalence of new HBV infection has definitely decreased due to universal vaccination programs but that of NAFLD has increased recently [24].

Predictions of HBsAg Seroclearance

In chronic HBV infections, HBsAg seroclearance reportedly occurs at a rate of 0.50–2.26%. Several factors have been suggested to be associated with seroclearance including age and HBeAg negativity. However, there are few studies evaluating whether HBV DNA levels are an independent predictor of HBsAg seroclearance.

Old age, a sustained inactive phase, and low levels of HBV DNA were the independent predictors of HBsAg

seroclearance [25]. The authors showed that HBsAg seroclearance occurred at a rate of 1.8% per year in HBeAg-negative chronic hepatitis B patients. In addition, multivariable analysis suggested that low HBV DNA levels, old age, and sustained inactive phase were independent predictors of HBsAg seroclearance, but use of antiviral agents was not. Therefore, spontaneous HBsAg seroclearance takes place in elderly patients with low serum HBV DNA levels (<2,000 IU/ml) who remain in a sustained inactive phase.

Non-B Non-C HCC

NBNC-HCC is associated with several etiologic factors such as alcoholic liver diseases (ALD) autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and NAFLD/nonalcoholic steatohepatitis. In addition, a variety of clinical factors are also involved in the development and progression of NBNC-HCC, including age, sex, alcohol consumption, and diabetes mellitus [26, 27]. There are only a few reports, however, on the clinical characteristics of NBNC-HCC, and the actual state of NBNC-HCC has not been fully elucidated [28–31].

Although the number of patients with NBNC-HCC has been increasing annually, many features of NBNC-HCC remain unknown. Based on the present study, the most common etiologic factor for NBNC-HCC was alcohol, and diabetes may be related to the occurrence of HCC in patients with non-alcohol-related liver disease. The comparison between groups revealed that non-ALD-HCC tended to be detected at a more advanced stage, whereas liver function in ALD-HCC was worse. Finally, the prognosis was equivalent between groups [32].

Conclusion

Tailor-made treatment for chronic hepatitis is a very important issue to be addressed even when new polymerase/protease inhibitors are available.

Disclosure Statement

The author has no conflict of interest to declare.

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