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EDITORIAL

Is the use of IL28B genotype justified in the era of interferon-free treatments for hepatitis C?

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Abstract

In 2009, several groups reported that interleukin-28B (IL28B) genotypes are associated with the response to peginterferon plus ribavirin therapy for chronic hepatitis C virus (HCV) infection in a genome-wide association study, although the mechanism of this association is not yet well understood. However, in recent years, tremendous progress has been made in the treatment of HCV infection. In Japan, some patients infected with HCV have the IL28B major genotype, which may indicate a favorable response to interferon-including regimens; however, certain patients within this group are also interferon-intolerant or ineligible. In Japan, interferon-free 24-wk regimens of asunaprevir and daclatasvir are now available for HCV genotype 1b-infected patients who are interferon-intolerant or ineligible or previous treatment null-responders. The treatment response to interferon-free regimens appears better, regardless of IL28B genotype. Maybe other interferon-free regimens will widely be available soon. In conclusion, although some HCV-infected individuals have IL28B favorable alleles, importance of IL28B will be reduced with availability of oral interferon free regimen.

Key words: Hepatitis C virus; Interleukin-28B; Interferon; Japan; Sustained virologic response

Core tip: Genome-wide association studies have revealed that interleukin-28B (IL28B) genotypes are associated with the response to interferon therapy for chronic hepatitis C. The mechanism of this association is not yet clear. Although many hepatitis C virus (HCV)-infected individuals have IL28B favorable alleles, in the near future, HCV-infected patients in Japan may be treated with interferon-free regimens, which avoid the adverse events caused by interferon plus ribavirin therapy.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of end-stage liver diseases and hepatocellular carcinoma (HCC) in Japan and the United States[1-4]. Chronic hepatitis C is an important health problem worldwide[5]. The eradication of HCV by interferon-including treatment could lead to the following benefits[6]: (1) fibrotic regression[7-9]; (2) reduction of HCC occurrence and recurrence[10-12]; (3) reduction of other complications, including liver failure, liver-related death[13,14] and liver-unrelated death[15]; and (4) improved quality of life[15]. A sustained virologic response (SVR), which is defined as HCV RNA negativity 24 wk after completion of antiviral therapy, could have beneficial effects in HCV-infected patients. In the era of direct-acting antivirals (DAA) against HCV, regimens including interferon remain important treatments for HCV eradication[5,16-33], although interferon-free regimens should be available worldwide soon[34]. In this review, we focused the distribution of interleukin-28B (IL28B) status in Japanese patients currently infected with HCV, and their treatment.

INTERLEUKIN-28B GENOTYPES

In 2009, several groups reported that a genetic polymorphism near the *IL28B* gene, which encodes interferon-lambda-3 (IL28B genotypes), was associated with the response to peginterferon plus ribavirin therapy for chronic hepatitis C in a genome-wide association study[35-37]. The IL28B minor genotype plays a crucial role in interferon resistance[38]. The host genetic polymorphism may be useful for predicting drug response[37,39]. IL28B major or minor genotype, respectively, could predict better or poor response to interferon therapy in patients infected with HCV. An association between inosine triphosphatase (ITPA) genetic variants and treatment-induced anemia has been reported in HCV-infected patients treated with peginterferon plus ribavirin[40-42]. ITPA major genotype could predict profound anemia induced by peginterferon plus ribavirin treatment in HCV-infected patients. A genetic polymorphism of interferon-lambda-4 has also been associated with the treatment response to interferon-including regimens for chronic hepatitis C infection[43-45]. Similar to IL28B genotypes, interferon-lambda-4 major or minor genotype, respectively, could predict better or poor response to interferon therapy in HCV-infected patients.

Mechanism of the association between the IL28B genotype and treatment response

Recently, Aoki *et al*[46] reported that serum IL28B levels are increased in patients with chronic hepatitis C, regardless of the IL28B genotype. They also suggested that serum IL28B is a biomarker of the activity and fibrosis of liver disease; however serum IL28B is not correlated with the responsiveness to peginterferon plus ribavirin therapy[46]. The same group reported that IL28B genotype affects IL28B production but that the outcome of peginterferon plus ribavirin treatment depends on the amount of IL28B protein[47].

Hepatic interferon-stimulated genes (ISGs) have been significantly associated with the IL28B polymorphism, and expression level of hepatic ISG was significantly higher in patients with the minor genotype than those with the major genotype[48,49]. Lagging *et al*[50] found that the favorable IL28B variants were associated with lower baseline plasma interferon-gamma-inducible protein-10 (IP-10), although high baseline levels of IP-10 predicted a slower first phase decline in HCV RNA and poor outcome following interferon plus ribavirin therapy in patients with chronic hepatitis C[51-53]. We also reported that IL28B genotypes and hepatic STAT1-nuclear translocation are independent predictors of treatment response[54]. IL28B overexpression in HepG2 cells induces ISGs that have been associated with the progression of HCV-related pathogenesis and antiviral activities against HCV[55]. Sugiyama *et al*[56] reported that the A (TA) dinucleotide repeat rs72258881 is associated with the transcriptional activity of IL28B. A functional polymorphism (rs4803217) in the 3' untranslated region (UTR) of IL28B has been shown to influence the AU-rich element (ARE)-mediated decay (AMD) of IL28B mRNA and binding of HCV-induced microRNAs during infection[57]. At the present, we do not know the precise mechanisms between IL28B variants and treatment response to interferon. Additional studies investigating these mechanisms are needed.

DISTRIBUTION OF IL28B GENOTYPES IN JAPANESE PATIENTS INFECTED WITH HCV

Kobayashi *et al*[58] analyzed IL28B genotypes in 1518 Japanese patients infected with HCV and reported that TT at rs8099917 and CC at rs12979860 as IL28B major genotypes were detected in 77.7% and 76.8% of patients, respectively, and that TG/GG at rs8099917 and CT/TT at rs12979860 as IL28B minor genotypes were detected in 22.3% and 23.2% of patients, respectively. Although there are some discrepancies between these two sets of genotypes, the linkage disequilibrium between two IL28B polymorphisms at rs8099917 and rs12979860 is strong in Japanese HCV patients[58]. In 2010, Akkarathamrongsin *et al*[59] found that genotyping by both rs8103142 and rs11881222 indicated that 77.9% and 22.1% of the patients had the major and minor genotypes, respectively. In 2011, we also reported that TT and TG/GG at rs8099917 as IL28B major and minor genotypes, respectively, were detected in 65.6% and 34.4% of HCV-infected patients, respectively[38]. Kurosaki *et al*[60] reported that TT and TG/

GG at rs8099917 as IL28B major and minor genotypes, respectively, were detected in 69.6% and 30.4% of HCV genotype 1-infected patients, respectively.

Thomas *et al*[61] reported that HCV clearance was observed much more frequently than expected (53%) in the CC IL28B genotypes at rs12979860, although the proportion of individuals with CT/TT IL28B genotypes at rs12979860 who cleared the virus (28%) was similar to a general population expectation, because HCV clearance occurs in approximately 30% of HCV-infected patients. Approximately 65%-70% of Japanese patients infected with HCV had the IL28B major genotype. In 2011, telaprevir, a first-generation HCV NS3/4A protease inhibitor with peginterferon plus ribavirin was introduced as treatment for HCV genotype 1 infection in Japan[22,45], and in 2013, simeprevir, a second-generation HCV NS3/4A protease inhibitor with peginterferon plus ribavirin was also made available in Japan[27,62]. We next examined the current status of IL28B genotypes in Japanese patients infected with HCV.

CURRENT DISTRIBUTION OF IL28B GENOTYPES IN JAPANESE PATIENTS INFECTED WITH HCV

The IL28B genotype is a strong predictor of treatment response in HCV-infected patients treated with interferon-including regimens. We examined the current status of the IL28B genotype rs8099917 distribution of the outpatients infected with HCV. Blood samples were obtained from 432 HCV-infected outpatients (mean age: 59.9 years, male/female: 224/208, HCV genotypes 1/2/3/unknown: 314/102/1/15) in our hospital. The IL28B genotype at rs8099917 was determined by TaqMan SNP genotyping assay using the Step One real-time PCR system (Applied Biosystems, Foster City, CA, United States). Clinical backgrounds, including the present status of HCV RNA positivity, were also examined. Written informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Chiba University, School of Medicine (number 508). Some patients had been included in previous studies[38,42,54,63-66].

Of the 432 patients, 301 and 131 had the IL28B major and minor genotypes, respectively (Figure 1A), and 87.7% were treated at least once with an interferon-including regimen, resulting in 184 SVR, 184 non-SVR, and 64 untreated/others, respectively. Of the 314 patients with HCV genotype 1, 218 and 96 had the IL28B major and minor genotypes, respectively (Figure 1B), and 122, 143, and 49 patients had SVR, non-SVR/untreated, or other, respectively. Of the 143 patients with HCV genotype 1 with non-SVR or untreated, 85 and 58 had the IL28B major and minor genotypes, respectively, and 22 (25.9%) of the 85 patients with HCV genotype 1 and the IL28B major type are now interferon-intolerant or ineligible. Of the 118 patients with HCV genotype non-1, 83 and 35 had the IL28B major and minor genotypes, respectively, and 62, 41, and 14 patients had SVR, non-SVR/untreated, or other, respectively. In the 41 patients with HCV genotype non-1 with non-SVR or untreated, 27 and 14 had the IL28B major and minor genotypes, respectively (Figure 1C), and 10 (37%) of the 27 patients with HCV genotype 1 and the IL28B major type are now interferon-intolerant or ineligible. The distribution of IL28B genotypes is not significantly different between HCV genotype 1 and non-1 (P = 0.947; Figure 1B and C).

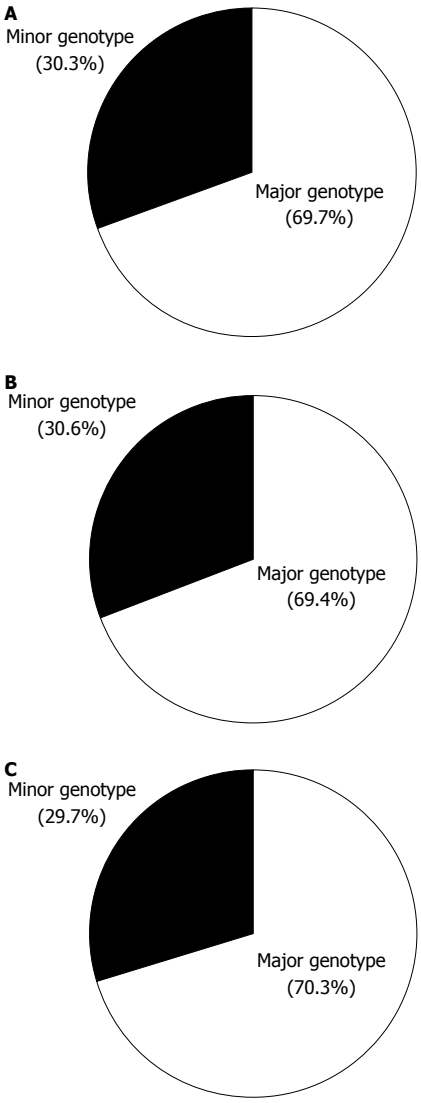

Figure 1 Distribution of interleukin-28B genotypes in Japanese patients infected with hepatitis C virus between February 2010 and April 2014. (A) Total patients (n = 432), (B) HCV genotype 1 patients (n = 314), and (C) HCV non-genotype 1 patients (n = 118). The white and black parts indicate the IL28B major and minor genotypes, respectively. IL28B: Interleukin-28B; HCV: Hepatitis C virus.

Thus, the patients infected with HCV genotypes 1 and non-1, who had IL28B minor genotypes in 40.6% (58/143) and 34.1% (14/41), respectively, should be treated. Further, some patients who had the IL28B major genotype are interferon-intolerant or ineligible. Regarding the current status of IL28B genotype rs8099917 distribution, we re-confirmed that the HCV-infected population in Japan should be treated with interferon-free regimens,

although interferon-including regimens may be effective in certain patients. The rs8099917 TT genotype may be significantly independently predictive of rapid virologic response, which is the single best predictor of SVR, in Asian HCV genotype patients[67].

CONCLUSION

In Japan, interferon-free 24-wk regimens of asunaprevir, a HCV NS3/4A inhibitor, and daclatasvir, a HCV NS5A inhibitor, can now be used for HCV genotype 1b-infected patients who are interferon-intolerant or ineligible, or previous-treatment null-responders[68-70]. In the near future, interferon-free 12-wk regimens of sofosbuvir plus ribavirin for HCV genotype 2-infected patients will be available[71]. Interferon-free 12-wk regimens of sofosbuvir, a HCV NS5B nucleotide polymerase inhibitor, and ledipasvir, a HCV NS5A inhibitor, for HCV genotype 1-infected patients will also be available[72]. The response to the treatment with interferon-free regimens appears to have no association with IL28B genotypes. In conclusion, although some HCV-infected individuals have IL28B favorable alleles, importance of IL28B will be reduced with availability of oral interferon free regimen.

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