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**interleukin****28B genetic polymorphism and hepatitis B virus infection**

Takahashi T. *IL28B* and HBV

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**Abstract**

interleukin(IL)28B genetic polymorphism is significantly associated with the sustained virological response rate in pegylated interferon-plus ribavirin treatment for chronic hepatitis C and also with spontaneous hepatitis C virus clearance. On the IL28B and the favorable outcome of chronic hepatitis B virus infection defined by HBeAg seroconversion, and/or hepatitis B surface antigen seroclearance in interferon or pegylated interferon-treatment, although the consensus has not been obtained. Several reports failed to show the positive association while some studies demonstrated it in certain settings of subjects. Indeed, more prospective studies in a large cohort are needed if any to determine a possible association between IL28B genetic polymorphism and the outcome of interferon or pegylated interferon-treatment for chronic hepatitis B.

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**Key words:** interleukin28B; Polymorphism; hepatitis B virus; Interferon; Pegylated interferon

**Core tip:** An association between interleukin (IL) 28B genetic polymorphism and sustained virological response rate of chronic hepatitis C by pegylated interferon-alpha and ribavirin treatment or spontaneous hepatitis C virus clearance has already been established. However, an association between IL28B and hepatitis B virus infection still remains unclear. We extensively discuss this topic and summarize the clinical data so far available.

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**Introduction**

Recent advances in molecular biology enable us to discover not only various factors in pathogens but also in hosts that may influence the fate, character, mode of onset or natural or therapeutic outcome of various disorders. One of such examples is a genome-wide analysis of sequence (G-WAS). Such progress is also obvious in the research field of gastroenterology and hepatology. A discovery of an association between single nucleotide polymorphism (SNP) at or near the interleukin28B gene (*IL28B*) and the sustained virological response (SVR) rate in pegylated interferon- (PEG-IFN) plus ribavirin (RBV) treatment for chronic hepatitis C (CH-C)[1-3] is an example. Subsequent studies confirmed an association between *IL28B* and spontaneous hepatitis C virus (HCV) clearance[4,5]. The *IL28B* genetic polymorphism can also account for the racial difference in the SVR rate in PEG-IFN/RBV treatment for CH-C[1].

Recently, a possible association of *IL28B* genetic polymorphism and hepatitis B virus (HBV) infection has become a target of an enthusiastic interest. It is well known that 240 million individuals are chronically infected worldwide with HBV[6], the majority in the Asia-Pacific region[7]. An association between *IL28B* genetic polymorphism and the rate of HBeAg seroconversion and/or hepatitis B surface antigen (HBsAg) seroclearance in PEG-IFN treatment has recently been argued intensively.

Here we summarize and discuss a possible association between *IL28B* genetic polymorphism and favorable outcome of chronic HBV infection defined by HBeAg seroconversion and/or HBsAg seroclearance in the treatment of chronic hepatitis B (CH-B) by PEG-IFN with or without nucleoside analogues.

**Facts on *IL28B***

*IL28B* is a class II cytokine receptor ligand related to type I interferons. These ligands play a critical role in response to microbial challenge and activate the JAK/STAT signaling system and shows anti-viral actions by inducing interferon-stimulated genes (ISG)[8]. *IL28B* is located on the long arm of chromosome 19 and spans about 1.5 kilo base pairs. It encodes interferon 3 (IFN 3), one of type III IFNs while *IL29* and *IL28A* encode other type III IFNs, namely IFN1 and 2.

It is still unknown why *IL28B* (namely IFN 3genetic polymorphism, influences the SVR in PEG-IFN/RBV therapy for CH-C as described above. Gene expression studies using peripheral blood mononuclear cells (PBMC) revealed that *IL28B* gene expression was lower in individuals carrying the minor alleles[2,3]. On the contrary, there is no difference in the hepatic *IL28B* gene expression according to haplotypes, although pretreatment intrahepatic ISG expressions are higher in individuals carrying the minor alleles[9,10]. These results may support the previously revealed facts that already elevated ISG gene expression before treatment was significantly related to poor viral eradication rate since externally given PEG-IFN could not fully stimulate ISG[11,12].

Type III IFN is a major component of innate immune system of liver cells. HCV infection studies in primary human fetal liver cell cultures (HFLC)[13] revealed that cell culture-induced HCV evoked expression of type III () IFNs and of ISGs while type I IFNs (IFN and ) were expressed scarcely. Higher levels of viral replication were associated with greater induction of ISGs and IFN. It has already been shown in 2005 that IFNinhibits HBV replication in a differentiated murine hepatocyte cell line as well as replication of a subgenomic and a full-length genomic HCV replicon in Huh7 cells[14]. IFN- and IFN3 in combination showed synergistic anti-HCV activity in the HCV 1b and 2a replicon system[15]. The humanized livers of chimeric mice exhibited increased expression at the mRNA and protein level of human IFNs, following treatment with a hepatotropic cationic liposome and a synthetic double-stranded RNA analog[16] resulting in strong antiviral effect on HBV and HCV. As to the possibility of IFN as therapeutic agents for CH-C, phase 1b trial revealed that weekly PEG-IFN-with or without daily RBV for 4 weeks was associated with clear antiviral activity across a broad range of doses in patients with CH-C[17].

As another source of IFN- in liver, human type 2 myeloid dendritic cells, or human blood dendritic cell antigen 3 (BDCA3)-positive cells instead of hepatocytes was recently reported to be a potent producer of IFN- in response to HCV[18,19].

**possible association of *IL28B* genetic polymorphism and spontaneous HBV recovery or outcome of PEG-IFN treatment for CH-B**

The first study concerning *IL28B* and HBV infection was reported in 2010, the next year of the discovery that this genetic polymorphism was strongly associated with the SVR rate of PEG/RBV for CH-C. In this report, C-C genotype of rs12979860 was not associated with HBV recovery (odds ratio 0.99)[20]. Two subsequent reports in 2011[21,22] also failed to show the possible association, although one revealed the association among genotype, allele and haplotype frequencies of *IL28B* with aminotransferase levels and HBV DNA[21]. In 2012, the first report that determined a positive association between *IL28B* genetic polymorphism and chronic HBV infection was published[23]. *IL28B* genotype was significantly associated with HBeAg seroconversion at the end of PEG-IFN treatment (*p <* 0.01), the adjusted odds ratio for seroconversion was 3.16 (*p =* 0.013) for AA *vs* AG/GG at rs12980275 after adjustment for HBV genotype, age, levels of HBV DNA and alanine aminotransferase, and PEG-IFN and, one of nucleoside analogues, lamivudine combination therapy. *IL28B* genotype was independently associated with an increased probability of HBeAg seroconversion during long-term follow-up (adjusted HR = 2.14, *p =* 0.018 by Cox regression analysis). Similar results were obtained for rs12979860. *IL28B* genotype was also associated with HBsAg clearance (HR, 3.47, *p =* 0.042). Thus, the authors concluded that polymorphisms near *IL28B* were independently associated with serologic response to PEG-IFN in patients with HBeAg-positive chronic hepatitis B.

Another report published in 2012[24] also demonstrated a possible association between IL28B and HBeAg-positive CH-B in Chinese Han population, while other 3 reports published in the same year, 2012[25-27] concluded that *IL28B* was not significantly related with the outcome of patients with CH-B who were treated with PEG-IFN. Three SNPs in the *IL28B* gene (rs12979869C/T, rs8099917G/T and rs12980275G/A) were examined in 330 subjects [including 154 HBV-related hepatocellular carcinoma (HCC) patients, 86 non-HCC patients with CH-B, 43 HBV self-limited infections and 47 healthy controls][28]. In conclusion, the *IL28B* rs12979860C/T polymorphism might affect susceptibility to the chronic HBV infection and progression of HCC. In another report, the effect of rs8099917 in *IL-28B* gene as well as rs187238 and rs1946518 in *IL-18* gene on HBV recurrence in liver transplant patients was investigated in Chinese Han population[29]. In 140 HBV-related liver transplant recipients, the genotype of *IL-28B* gene rs8099917 was associated with aminotransferase levels. The recipients with allele G (GG + GT) had higher aminotransferase levels (*p <* 0.05). No association was found between *IL-18* gene and *IL28B* gene polymorphisms with HBV recurrence in the liver transplant recipients or the donors. The authors concluded that allele G of rs8099917 was associated with hepatitis B-related hepatocyte injury. Association analysis between SNPs in *IL-28B* gene and the progress of HBV infection in Han Chinese revealed[30] that *IL-28B* rs12979860 C/T polymorphism T allele appeared to be more prevalent in patients with hepatocellular carcinoma (HCC) than in liver cirrhosis (LC).

In 2013, a positive association between *IL-28B* genetic polymorphism and the outcome of CH-B[31] was reported. A hundred and one HBeAg-negative patients (92% genotype D) with compensated CH-B were followed for a median of 11 (1-17) years after median 23 (10-48) mo of either standard or pegylated IFN- therapy. The rs12979860 (C > T) genotype in the *IL28B* locus was assessed. During a median of 11 years of post-treatment follow-up, 21 (21%) patients cleared serum HBsAg, including 15 who developed > 10 IU/ml anti-HBs titers. Forty-eight patients (47%) had CC genotype, 42 (42%) CT and 11 (11%) TT, the allelic frequency being 68% for C allele and 32% for T allele. The rate of serum HBsAg clearance was 29% (*n* = 14) in CC compared to 13% (*n* = 7) in non-CC genotype carriers (*p =* 0.039). Baseline HBV DNA levels < 6 log cp/ml (OR = 11.9, 95%CI: 2.8-50.6, *p =* 0.001), ALT levels >136 IU/ml (OR = 6.5, 95%CI: 1.8-22.5, *p =* 0.003), duration of IFN (OR = 1.16, 95%CI: 1.02-1.31, *p =* 0.021) and genotype CC (OR = 3.9, 95%CI: 1.1-13.2, *p =* 0.025) independently predicted HBsAg clearance. The authors concluded that *IL28B* polymorphism is an additional predictor of off-therapy IFN-related HBsAg seroclearance in HBeAg-negative patients chronically infected by genotype D HBV. Another work published in 2012[32] revealed HLA-DP and IL28B genetic polymorphisms were associated with spontaneous HBsAg seroclearance in chronic hepatitis B patients.

In 2013, two reports concerning *IL28B* genetic polymorphism and the therapeutic outcome by PEG-IFN or natural course of CH-B failed to show any meaningful association between both[33,34]. On the contrary, the SNP upstream of *IL28B* that has the strongest genetic association with HCV recovery had an inverse influence on HBV recovery[35] in a recent Korean study. *IL28B* polymorphism correlated with active hepatitis in patients with HBeAg-negative CH-B[36]. Jilg *et al*[37] describes and summarizes potent associations between *IL28B* genetic polymorphism and chronic HBV infection in their review. Table 1 summarizes a possible association between *IL28B* genetic polymorphism and the effect of interferon- or PEG-IFN in hepatitis B virus infection, or spontaneous HBsAg seroclearance.

**Future perspective**

As mentioned above, a lot of controversies are still arising concerning an true association between *IL28B* genetic polymorphism and chronic HBV infection. We need more evidences to obtain a final conclusion and a lot of prospective studies with large cohorts of patients would be needed for accomplishing this purpose.

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**Table 1** possible association between IL28B genetic polymorphism and the effect of interferon-a and/or pegylated interferon-a, or spontaneous HBeAg and/or HBsAg clearance in hepatitis B virus infection.

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| --- |
|  |
| No | year | ref. | targeted SNPs | subject settings | HBe | result | comments |
| 1 | 2010 | Martin *et al*[20] | rs12979860 | 226 HBV persistance, 384 HBV recovery | nd | negative | C/C genotype of rs12979860 was not associated with HBV recovery (OR = 0.99)  |
| 2 | 2011 | Li *et al*[21] | rs12979860, rs12980275, rs8099917 | 203 chronic HBV infection, 203 self-limited HBV infection, 203 individuals negative for all HBV seromarkers (Chinese han population) | nd | netative |  |
| 3 | Tseng *et al*[22] | IL28B regions | 115 HBeAg-positive chronic hepatitis B patients | positive | negative |  |
| 4 | 2012 | Sonneveld *et al*[23] | rs12980275, rs12979860 | 205 HBeAg-positive patients who were treated with PEG-IFN (Europeans and Asians) | positive | positive | IL28B genotype was significantly assciated with HBeAg seroconversion at the end of treatment (*p <* 0.001, OR = 3.16), during long-term follow up (HR = 2.14), or with HBsAg seroclearance (HR = 3.47).  |
| 5 | Wu *et al*[24] | rs8099917 | 512 HBeAg positive chronic hepatitis B patients (Han Chinese) were treated with pegylated interferon a-2a ± nucleoside analogues | positive | positive | The frequency of G allele of rs8099917 was significantly higher in response group than in non response group (8.3% *vs* 3.9%, *p =* 0.003, OR = 0.44, 95%CI: 0.25-0.79). The genotype distributions of this SNP also differed significantly between two groups (*p =* 0.003). |
| 6 | de Niet *et al*[25] | rs12979860 | 95 chronic hepatitis B patients who were treated with PEG-IFN and adefovir for 1year and who had 15% HBsAg loss (overall) | positive and negative | negative |  |
| 7 | Peng *et al*[26] | rs12979860 | 651 HBV persistent infection (387 with liver cirrhosis, 264 without cirrhosis), 226 healthy individuals who recovered from HBV infection. | nd | negative | No association with clearance of HBsAg, HBeAg, HBV DNA level, apparent hepatitis onset and liver cirrhosis (*p* > 0.05).  |
| 8 | 2013 | Lampertico *et al*[31] | rs12979860 | 101 HBeAg-negative patients (92% genotype D) with compensated chronic hepatitis B (84% males, 42% with cirrosis) | negative | positive | The rate of serum HBsAg clearance was 29% in CC (major homo) compared to 13% in non-CC (hetero or minor homo) genotype carriers (*p =* 0.039). |
| 9 | Seto *et al*[32] | IL28B (rs12979860, rs8099917) | 203 chronic hepatitis B patients achieving spontaneous HBsAg seroclearance with 203 age- and sex-matched chronic hepatitis B patients without HBsAg seroclearance (control) | negative | positive | IL28B haptotype block CG was assiciated with HBsAg seroclearance (OR = 10.5, *p =* 0.026). |
| 10 | Holmes *et al*[33] | rs12979860 | 96 patients (88% were Asian, 62% were HBeAg positive and 13% were METAVIR stage F3-4). The majority (84%) of patients carried the CC IL28B genotype (major homo) | positive and negative | negative |  |
| 11 | Lee *et al*[34] | rs8099917, rs12979860, rs12980275 | 404 spontaneously recovered patients, 313 chronic hepatitis B patients, 305 liver cirrhosis patients and 417 hepatocellular carcinoma patients | nd | negative |  |
| Studies are chronologically numbered. HBV: hepatitis B virus; nd: Not determined or not described. |