Interleukin 28B genetic polymorphism and hepatitis B virus infection

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INTRODUCTION

Recent advances in molecular biology have enabled us to discover not only various factors regarding pathogens, but also regarding hosts which may influence the fate, character, mode of onset and natural or therapeutic outcome of various disorders. One such example is a genome-wide analysis of sequence. Such progress is also obvious in the research field of gastroenterology and hepatology. For example, the discovery of an association between single nucleotide polymorphism (SNP) at or near the interleukin 28B (IL28B) gene and the sustained virological response (SVR) rate with pegylated interferon-α (PEG-IFN) plus ribavirin (RBV) treatment for chronic hepatitis C (CH-C) [1-3]. Subsequent studies confirmed an association between IL28B and spontaneous hepatitis C virus clearance [4,5]. The IL28B genetic polymorphism also accounts for the racial difference in the SVR rate with PEG-IFN/RBV treatment for CH-C [1].

Recently, a possible association between IL28B genetic polymorphism and hepatitis B virus (HBV) infection has become a target of interest. It is known that 240 million
individuals are chronically infected with HBV worldwide[9], with the majority in the Asia-Pacific region[7]. An association between IL28B genetic polymorphism and the rate of hepatitis B e antigen (HBeAg) seroconversion and/or hepatitis B surface antigen (HBsAg) seroconversion with PEG-IFN treatment has been intensively discussed recently.

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

### FACTS ON IL28B

IL28B is a class 1 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 show anti-viral activity 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 lambda 3 (IFN λ3), one of the type III IFNs, while IL29 and IL28A encode other type III IFNs, namely IFN λ1 and λ2.

It is unknown why IL28B (namely IFN λ3) genetic polymorphism influences the SVR in PEG-IFN/RBV therapy for CH-C as described above. Gene expression studies using peripheral blood mononuclear cells revealed that IL28B gene expression was lower in individuals carrying minor alleles[21,22]. In contrast, there is no difference in hepatic IL28B gene expression according to haplotypes, although pretreatment intrahepatic ISG expressions are higher in individuals carrying minor alleles[23,24]. These results may support the previously reported findings that already elevated ISG gene expression before treatment was significantly related to poor viral eradication rate since externally administered PEG-IFN did not fully stimulate ISG[11,13].

Type III IFN is a major component of the innate immune system of liver cells. HCV infection studies in primary human fetal liver cell cultures[18] revealed that cell culture-induced HCV evoked expression of type III (λ) IFNs and of ISGs, while low expression of type I IFNs (IFN α and β) was observed. Higher levels of viral replication were associated with greater induction of ISGs and IFNλ. It was shown in 2005 that IFNλ inhibited 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-α and IFNλ3 in combination showed synergistic anti-HCV activity in the HCV 1b and 2a replicon systems[15]. The humanized livers of chimeric mice exhibited increased expression at the mRNA and protein level of human IFNλs, following treatment with a hepatotropic cationic lisosome and a synthetic double-stranded RNA analog[16] resulting in a strong antiviral effect on HBV and HCV. With regard to the possibility of IFNλ as a therapeutic agent for CH-C, a phase 1b trial revealed that weekly PEG-IFN-λ with or without daily RBV for 4 wk was associated with clear antiviral activity across a broad range of doses in patients with CH-C[17].

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

### POSSIBLE ASSOCIATION BETWEEN 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 following year it was discovered that this genetic polymorphism was strongly associated with the SVR rate in patients with CH-C treated with PEG/RBV. In this report, C-C genotype of rs12979860 was not associated with HBV recovery (OR = 0.99)[20]. Two subsequent reports in 2011[21,22] also failed to show the possible association, although one revealed an association between genotype, allele and haplotype frequencies of IL28B and both 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 a nucleoside analogue-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 HBsAg-positive chronic hepatitis B.

Another report published in 2012[24] also demonstrated a possible association between IL28B and HBeAg-positive CH-B in a Chinese Han population, while another 3 reports published in the same year[25-27] concluded that IL28B was not significantly related to the outcome of patients with CH-B who were treated with PEG-IFN. Three SNPs in the IL28B gene (rs12979860C/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 chronic HBV infection and progression of HCC. In another report, the
Table 1  Possible association between interleukin 28B genetic polymorphism and the effect of interferon-α and/or pegylated interferon-α, or spontaneous hepatitis B e antigen and/or hepatitis B surface antigen clearance in hepatitis B virus infection

| No. | Year | Ref. | Targeted SNPs | Subject settings | HBe | Result | Comments |
|-----|------|------|---------------|-----------------|-----|--------|----------|
| 1   | 2010 | Martin et al[21] | rs12979860 | 226 HBV persistence, 384 HBV recovery | ND | Negative | C/C genotype of rs12979860 was not associated with HBV recovery (OR = 0.99) |
| 2   | 2011 | Li et al[22] | rs12979860, rs12980275, rs8099917 | 203 chronic HBV infection, 203 self-limited HBV infection, 203 individuals negative for all HBV seromarkers (Chinese Han population) | ND | Negative | |
| 3   | 2011 | Tseng et al[23] | IL28B regions | 115 HBeAg-positive chronic hepatitis B patients | Positive | Negative | IL28B genotype was significantly associated 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) |
| 4   | 2012 | Sonneveld et al[24] | rs12980275, rs12979860 | 205 HBeAg-positive patients who were treated with PEG-IFN (Europeans and Asians) | Positive | Positive | The frequency of G allele of rs8099917 was significantly higher in the response group than in the non-response group (8.5% 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 the two groups (P = 0.003) |
| 5   | 2012 | Wu et al[25] | rs8099917 | 512 HBeAg-positive chronic hepatitis B patients (Han Chinese) were treated with pegylated interferon a-2a + nucleoside analogues | Positive | Positive | |
| 6   | 2012 | de Niet et al[26] | rs12979860 | 95 chronic hepatitis B patients who were treated with PEG-IFN and adefovir for 1 yr and who had 15% HBsAg loss (overall) | Positive and negative | Negative | No association with clearance of HBsAg, HBcAg, HBV DNA level, apparent hepatitis onset and liver cirrhosis (P > 0.05) |
| 7   | 2012 | Peng et al[27] | rs12979860 | 651 HBV persistent infection (387 with liver cirrhosis, 264 without cirrhosis), 226 healthy individuals who recovered from HBV infection | ND | Negative | 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) |
| 8   | 2013 | Lampertico et al[28] | rs12979860 | 101 HBeAg-negative patients (92% genotype D) with compensated chronic hepatitis B (84% males, 42% with cirrhosis) | Negative | Positive | IL28B haplotype block CG was associated with HBsAg seroclearance (OR = 10.5, P = 0.026) |
| 9   | 2013 | Seto et al[29] | 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 | |
| 10  | 2013 | Holmes et al[30] | rs12979860 | 96 patients (88% were Asian, 62% were HBeAg positive and 13% were METAVIR stage F3-F4). The majority (84%) of patients carried the CC IL28B genotype (major homo) | Positive and negative | Negative | |
| 11  | 2013 | Lee et al[31] | 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; IL: Interleukin; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; PEG-IFN: Pegylated interferon-α.

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 a Chinese Han population[21]. 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 *IL-28B* 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 HCC than in those with liver cirrhosis.

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 a median of...
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