Original article

Interleukin 28B genetic polymorphisms and viral factors help identify HCV genotype-1 patients who benefit from 24-week pegylated interferon plus ribavirin therapy

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Background: Interleukin 28B (IL28B) single nucleotide polymorphism (SNP) genotypes and viral factors can predict sustained virological response (SVR) in HCV genotype-1 (HCV-1) patients receiving 48 weeks of pegylated interferon and ribavirin. Whether these factors would identify those patients who can benefit from a shorter duration of therapy remains unclear.

Methods: Treatment-naive HCV-1 patients (n=662) receiving 24 or 48 weeks of combination therapy were enrolled. Baseline demographic data, HCV viral load, IL28B SNP genotypes (rs8099917), duration of therapy and rapid virological response (RVR) were evaluated to predict SVR. The SVR rates were further stratified by the independent factors and compared.

Results: The IL28B rs8099917 TT genotype, low baseline viral load (HCV RNA≤600,000 IU/ml), RVR and 48-week therapy independently predicted SVR. In RVR patients with the IL28B rs8099917 TT genotype, the SVR rate of 24-week therapy was comparable to 48-week therapy (95% versus 99%; P=0.21) at low baseline viral load, but was inferior to 48-week therapy (70% versus 97%; P<0.001) at high baseline viral load. In non-RVR patients, the SVR rate of 24-week therapy was inferior to 48-week therapy for those with the IL28B rs8099917 TT genotype but high baseline viral load (23% versus 62%; P<0.001), and those with the IL28B rs8099917 GT/GG genotype but low baseline viral load (0% versus 33%; P=0.02).

Conclusions: HCV-1 patients simultaneously bearing the IL28B rs8099917 TT genotype, low baseline viral load and RVR can benefit from a shorter duration of combination therapy.

Introduction

Chronic HCV infection, the leading cause of cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), affects approximately 170 million individuals worldwide [1]. Pegylated interferon (PEG-IFN) plus ribavirin (RBV) therapy is the standard of care (SOC) for chronic HCV infection, with the overall sustained virological response (SVR) rates of 38–79% in HCV genotype-1 (HCV-1) patients [2–8]. In addition, East Asian HCV-1 patients have been shown to have a better SVR rate than Western patients (76–79% versus 39–52%) [2–8]. However, a significant proportion of HCV-1 patients is still not responsive to the SOC and requires novel treatment. Recent studies consistently showed that adding direct-acting antivirals to the current
SOC can improve the SVR rates in treatment-naive and treatment-experienced HCV-1 patients [9–14]. Many pretreatment factors, including age, gender, body mass index (BMI), insulin resistance, hepatic steatosis/fibrosis, ethnicity and viral load, are associated with SVR [15]. Furthermore, the undetectable viral load at week 4 of treatment (rapid virological response [RVR]) is highly predictive of SVR. A recent meta-analysis suggested that HCV-1 patients with low baseline viral load (≤400,000 IU/ml) and an RVR could shorten their treatment duration from 48 to 24 weeks without compromising SVR rates [16]. However, the effect of other pretreatment factors deserves further study and could strengthen this suggestion. Recently, the single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene (rs8099917 and rs12979860), which is located on chromosome 19 and encodes interferon (IFN)-λ3, is highly associated with improved early viral kinetics as well as spontaneous or treatment-induced viral clearance in HCV-1 patients [17–25]. However, the role of IL28B SNP genotypes and viral factors in identifying HCV-1 patients who can benefit from shorter duration of SOC remains unknown. This is particularly relevant in East Asian patients because most of them have a favourable IL28B SNP genotype and thus a better response to the current SOC than Western patients [26,27]. In this study, we aimed to define the effect of host and viral factors on the SVR rates in East Asian HCV-1 patients who received 24 or 48 weeks of combination therapy.

Methods

Patients
Treatment-naive chronic HCV-1 patients who participated in clinical studies between 2006 and 2010 in Taiwan, in which patients were randomly assigned to receive 24 or 48 weeks of PEG-IFN-α2a (180 μg/week; Pegasys, Hoffman-LaRoche, Basel, Switzerland) and RBV (1,000–1,200 mg/day; Copegus, Hoffman-LaRoche; 1,000 mg/day for <75 kg and 1,200 mg/day for ≥75 kg), were enrolled [6,23,28,29]. Chronic HCV infection was defined by the presence of anti-HCV antibody (Abbott HCV EIA 3.0; Abbott Laboratories, Abbott Park, IL, USA) and serum HCV RNA by real-time (RT)-PCR analysis (Cobas TaqMan HCV Test v2.0; Roche Diagnostics GmbH, Mannheim, Germany; limit of detection 15 IU/ml) for ≥6 months. Patients without available serum HCV RNA data at weeks 4 and 12 of treatment, at the end of treatment and at 24 weeks after the end of treatment to determine on-treatment and off-therapy virological responses, or without available human genomic DNA for IL28B SNP genotype analysis, who failed to receive ≥80% of both PEG-IFN and RBV doses and ≥80% of expected treatment duration (80/80/80 rule) [30], or who refused to provide informed consent were excluded from the study.

Study design
Pretreatment demographics, hemogram, albumin, bilirubin, alanine aminotransferase (ALT) level, HCV RNA, HCV genotype (Inno-LiPA HCV II; Innogenetics, Ghent, Belgium), and staging of hepatic fibrosis by METAVIR score (F0–F4) [31] were extracted from the database. Serial serum HCV RNA levels were determined by RT-PCR analysis (Cobas TaqMan HCV Test v2.0, limit of detection 15 IU/ml) at weeks 4 and 12 of treatment, at the end of treatment and at week 24 after the end of treatment. RVR, end-of-treatment virological response (ETVR), and SVR were defined as undetectable serum HCV RNA at week 4 of treatment, at the end of treatment, and at week 24 after the end of treatment. Early virological response (EVR) was defined as ≥2-log reduction of serum HCV RNA from pretreatment to week 12 of treatment. All patients who failed to achieve EVR were allowed to receive further treatment to 24 weeks to confirm non-response or slow-response. Furthermore, patients who were assigned to 48 weeks of treatment but remained detectable HCV RNA at week 24 of treatment were considered non-responders and stopped further treatment. Patients with viral relapse (serum HCV RNA was undetectable at the end of treatment but became detectable at the end of follow-up), viral breakthrough (serum HCV RNA was detectable during the treatment, but once undetectable at earlier treatment), and viral non-response (serum HCV RNA was never undetectable during the treatment) were considered as failure to achieve SVR. Although patients who were assigned to 48-week treatment but who had viral breakthrough or viral non-response at week 24 of treatment stopped further treatment, they were eligible for the analyses despite not meeting the 80/80/80 rule. The baseline HCV RNA levels of ≤600,000 IU/ml and >600,000 IU/ml were defined as low and high viral load, respectively [17,22]. Significant hepatic fibrosis was defined as a fibrosis stage of ≥F2 by METAVIR score.

Human genomic DNA was extracted from peripheral blood mononuclear cells by QIAamp kits (Qiagen, Inc., Valencia, CA, USA). IL28B SNP (rs8099917) genotypes (homozygous TT, heterozygous GT and homozygous GG genotypes) were analysed by the ABI TaqMan allelic discrimination kit and the ABI 7900HT Sequence Detection System (Applied Biosystems, Life Technologies Corporation, Grand Island, NY, USA) [23].

The protocol was approved by the Ethical Committee and was conducted in accordance with the principles of the Declaration of Helsinki and International
Conference on Harmonization for Good Clinical Practice. Written informed consent was obtained from each patient before enrolment.

Statistical analyses

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 17.0; SPSS Inc., Chicago, IL, USA). Patient characteristics were expressed as mean ± standard deviation and percentage when appropriate. The Hardy–Weinberg equilibrium χ² test was assessed by Haplovew software to evaluate, in the eligible patients, the IL28B rs8099917 genotype deviation from expectation [32]. Univariate analyses of pretreatment and on-treatment factors by two-sample t-test and χ² test with Fisher’s exact test were performed to discriminate patients with or without SVR. Factors with P-values of ≤0.10 by univariate analysis entered into multivariate logistic regression analysis to find independent factors, which were expressed by odds ratio (OR) with 95% confidence interval (CI), to predict SVR. The stratified SVR rates by various independent factors were compared using χ² with Fisher’s exact test. All statistical tests were two-tailed and the results were considered statistically significant when a P-value was <0.05.

Results

Patient characteristics

Of 791 HCV-1 patients enrolled (24-week group: n=395; 48-week group: n=396), 129 (16.3%) were excluded from the study because of unavailable HCV RNA data to determine virological responses in 31 (24-week group: 15; 48-week group: 16), failure to meet 80/80/80 rule in 81 (24-week group: 33; 48-week group: 48), unavailable human genomic DNA samples for IL28B SNP genotype analysis in 11 (24-week group: 6; 48-week group: 5), and unwilling to provide informed consent in 6 (24-week group: 3; 48-week group: 3). The remaining 662 patients assigned to 24-week (n=338) or 48-week (n=324) therapy were eligible for the study. Table 1 shows the patient characteristics. The pretreatment patient characteristics were comparable between 24-week and 48-week groups. Of the patients in the study, 266 (40.1%) had a low baseline

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>24-week treatment (n=338)</th>
<th>48-week treatment (n=324)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 ±10</td>
<td>54 ±11</td>
<td>0.52</td>
</tr>
<tr>
<td>Age ≥60 years, n (%)</td>
<td>101 (29.9)</td>
<td>84 (25.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>192 (58.8)</td>
<td>186 (57.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.6 ±3.6</td>
<td>25.4 ±3.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>14.6 ±1.5</td>
<td>14.4 ±1.5</td>
<td>0.87</td>
</tr>
<tr>
<td>White blood cell, ×10⁶/l</td>
<td>5.5 ±1.7</td>
<td>5.4 ±1.6</td>
<td>0.89</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/l</td>
<td>173 ±55</td>
<td>173 ±57</td>
<td>0.93</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.2 ±0.3</td>
<td>4.3 ±0.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Bilirubin total, mg/dl</td>
<td>0.9 ±0.4</td>
<td>1.0 ±0.4</td>
<td>0.42</td>
</tr>
<tr>
<td>ALT quotient/ULN</td>
<td>3.8 ±3.0</td>
<td>3.6 ±2.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline HCV RNA level, log₁₀ IU/ml</td>
<td>5.9 ±0.7</td>
<td>5.8 ±0.7</td>
<td>0.26</td>
</tr>
<tr>
<td>Baseline HCV RNA level ≤600,000 IU/ml, n (%)</td>
<td>136 (40.2)</td>
<td>130 (40.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>1a, n (%)</td>
<td>13 (3.9)</td>
<td>10 (3.1)</td>
<td></td>
</tr>
<tr>
<td>1b, n (%)</td>
<td>310 (91.7)</td>
<td>301 (92.9)</td>
<td></td>
</tr>
<tr>
<td>1a+1b, n (%)</td>
<td>15 (4.4)</td>
<td>13 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Significant hepatic fibrosis, METAVIR ≤F2</td>
<td>265 (78.4)</td>
<td>247 (76.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>IL28B rs8099917 genotype</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>TT, n (%)</td>
<td>273 (80.8)</td>
<td>263 (81.2)</td>
<td></td>
</tr>
<tr>
<td>GT/GG, n (%)</td>
<td>65 (19.2)</td>
<td>61 (18.8)</td>
<td></td>
</tr>
<tr>
<td>RVR rate, n (%)</td>
<td>184 (54.4)</td>
<td>179 (55.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>SVR rate, n (%)</td>
<td>176 (52.1)</td>
<td>240 (74.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained virological response, n (%)</td>
<td>176 (52.1)</td>
<td>240 (74.1)</td>
<td></td>
</tr>
<tr>
<td>Viral relapse, n (%)</td>
<td>149 (44.0)</td>
<td>69 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Viral breakthrough, n (%)</td>
<td>3 (0.9)</td>
<td>9 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Non-response, n (%)</td>
<td>10 (3.0)</td>
<td>6 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are shown as ± standard deviation unless otherwise indicated. ALT, alanine aminotransferase; IL28B, interleukin 28B; IU, international unit; RVR, rapid virological response; SVR, sustained virological response; ULN, upper limit of normal.
Table 2. Univariate and multivariate logistic regression analyses of pretreatment and on-treatment factors to predict sustained virological response

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration, 48 versus 24 weeks, n (%)</td>
<td>SVR [n=416]</td>
<td>Non SVR [n=246]</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>Age, ≤60 versus &gt;60 years, n (%)</td>
<td>240/176 (58/42)</td>
<td>84/162 (34/66)</td>
<td>&lt;0.001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gender, female versus male, n (%)</td>
<td>311/105 (75/25)</td>
<td>166/80 (67/33)</td>
<td>0.08</td>
<td>1.10 (0.55, 1.49)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>14.5 ±1.4</td>
<td>14.4 ±1.6</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>White blood cell count, x10³/l</td>
<td>5.5 ±1.7</td>
<td>5.3 ±1.6</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Platelet count, x10⁹/l</td>
<td>182 ±58</td>
<td>158 ±49</td>
<td>0.01</td>
<td>1.01 (0.98, 1.03)</td>
</tr>
<tr>
<td>ALB, bilirubin total, mg/dl</td>
<td>4.3 ±0.3</td>
<td>4.1 ±0.3</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>ALT quotient</td>
<td>3.8 ±2.9</td>
<td>3.5 ±2.7</td>
<td>0.10</td>
<td>1.03 (0.94, 1.13)</td>
</tr>
<tr>
<td>Baseline HCV RNA level, ≤600,000 versus &gt;600,000 IU/ml, n (%)</td>
<td>219/197 (53/47)</td>
<td>47/199 (19/81)</td>
<td>&lt;0.001</td>
<td>3.69 (2.08, 6.57)</td>
</tr>
<tr>
<td>HCV genotype, 1a versus 1b versus 1a+1b, n (%)</td>
<td>16/384/16 (14/92/4)</td>
<td>7/227/12 (3/92/5)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>IL28B rs8099917 genotype, TT versus GT/GG, n (%)</td>
<td>388/28/83 (93/7)</td>
<td>148/98 (60/40)</td>
<td>&lt;0.001</td>
<td>12.34 (6.46, 23.60)</td>
</tr>
<tr>
<td>Significant hepatic fibrosis, yes versus no, n (%)</td>
<td>307/109 (74/24)</td>
<td>205/41 (83/17)</td>
<td>0.005</td>
<td>0.85 (0.45, 1.58)</td>
</tr>
<tr>
<td>RVR, yes versus no, n (%)</td>
<td>325/91 (78/22)</td>
<td>38/208 (15/85)</td>
<td>&lt;0.001</td>
<td>15.24 (8.91, 26.06)</td>
</tr>
</tbody>
</table>

Values are shown as ± standard deviation unless otherwise indicated. Factors with a P-value ≤0.10 by univariate analysis were entered into multivariate logistic regression analysis. ALT, alanine aminotransferase; IL28B, interleukin 28B; IU, international unit; OR, odds ratio; RVR, rapid virological response; SVR, sustained virological response; ULN, upper limit of normal.

Figure 1. The positive predictive value of the IL28B rs8099917 TT genotype, low baseline viral load and presence of RVR for SVR

Low viral load: baseline HCV RNA<600,000 IU/ml. The numerators at the base of the bar indicate the number of patients with sustained virological response (SVR); the denominators at the base of the bar indicate the total number of patients. PPV, positive predictive value; RVR, rapid virological response.

viral load. The genotype analysis showed that 536 patients (81.0%) bear the IL28B rs8099917 TT genotype, and the remaining 126 (19.0%) bear the IL28B rs8099917 GT/GG genotypes. The genotype results in Hardy–Weinberg disequilibrium showed the eligible patients did not deviate from expectation (χ²=1.09, P=0.58). The RVR rates were comparable in 24-week (54.4%) and 48-week (55.2%) groups (P=0.88). In contrast, the SVR rate was significantly higher in 48-week (74.1%) than that in 24-week (52.1%) groups (P<0.001).

Predictive factors for SVR

Table 2 shows the univariate and multivariate analyses to predict SVR. By univariate analysis, treatment duration (P<0.001), age (P=0.08), platelet count (P=0.01), ALT quotient (P=0.10), baseline HCV RNA level (P<0.001), IL28B rs8099917 genotype (P<0.001), significant hepatic fibrosis (P=0.005) and RVR (P<0.001) were associated with SVR. Multivariate analysis showed that 48-week treatment (OR 6.66; 95% CI 3.97, 11.18; P<0.001), low baseline viral load (OR 3.69; 95% CI 2.08, 6.57; P<0.001), IL28B rs8099917 TT genotype (OR 12.34; 95% CI 6.46, 23.60; P<0.001) and RVR (OR 15.24; 95% CI 8.91, 26.06; P<0.001) were independent predictors for SVR. The positive predictive value (PPV) of IL28B rs8099917 TT genotype, low baseline viral load, and RVR for SVR was 69%, 82% and 90%, respectively. Furthermore, the PPV of IL28B rs8099917 TT genotype, low baseline viral load, and RVR for SVR was 62%, 77% and 82% in patients with 24-week therapy, and 82%, 84% and 98% in those with 48-week therapy (Figure 1).

RVR rates stratified by IL28B rs8099917 genotypes and baseline viral load

Because RVR was the most important factor for SVR, the RVR rates were further evaluated in patients with different baseline viral load and IL28B SNP genotype (Figure 2). The RVR rate was significantly higher in patients with the IL28B rs8099917 TT genotype than
those with the GT/GG genotype (62% versus 25%; P<0.001), or in patients with low baseline viral load than those with high baseline viral load (80% versus 38%, respectively; P<0.001). In patients with the IL28B rs8099917 TT genotype, the RVR rate of patients with a low baseline viral load was significantly higher than that of those with a high baseline viral load (89% versus 43%, respectively; P<0.001). A similar phenomenon was found in patients with the IL28B rs8099917 GT/GG genotype (40% for a low baseline viral load versus 16% for a high baseline viral load; P=0.005).

Furthermore, the RVR rate of patients with the IL28B rs8099917 TT genotype was significantly higher than that of those with IL28B rs8099917 GT/GG genotype in terms of low (89% versus 40%, P<0.001) and high (43% versus 16%; P<0.001) baseline viral loads.

SVR rates stratified by IL28B SNP genotypes, baseline viral load and treatment duration in RVR patients

In RVR patients, the SVR rate of 48-week therapy was significantly higher than that of 24-week therapy for those with the IL28B rs8099917 TT genotype (98% versus 85%; P<0.001), IL28B rs8099917 GT/GG genotype (94% versus 50%; P=0.02) or high baseline viral load (96% versus 66%; P<0.001), but the SVR rates were comparable for those with low baseline viral load (99% versus 92%; P=0.06). For patients with 24-week therapy, the SVR rate was significantly higher for those with the IL28B rs8099917 TT genotype than for those with the GT/GG genotype (85% versus 50%; P<0.001), or in those with low baseline viral load than in those with high baseline viral load (92% versus 66%; P<0.001). For patients with 48-week therapy, the RVR rate for those with the IL28B rs8099917 TT genotype was comparable with that for those with the GT/GG genotype (98% versus 94%; P=0.32), or for those with low baseline viral load to those with high baseline viral load (99% versus 96%; P=0.31; Figure 3A).

Figure 3A also shows the stratified SVR rates by IL28B SNP genotypes, baseline viral load and treatment duration in RVR patients. In patients with low baseline viral load, the SVR rates of 48- and 24-week therapies were comparable for those with the IL28B rs8099917 TT genotype (99% versus 95%, P=0.21) or GT/GG genotype (100% versus 64%, P=0.10). In patients with a high baseline viral load, the SVR rate of 48-week therapy was significantly higher than that of 24-week therapy for those with the IL28B rs8099917 TT genotype (97% versus 70%; P<0.001) or GT/GG genotype (88% versus 20%; P=0.03).

SVR rates stratified by IL28B SNP genotypes, baseline viral load and treatment duration in non-RVR patients

In non-RVR patients, the SVR rate of 48-week of therapy was significantly higher than that of 24-week therapy for those with IL28B rs8099917 TT genotype (60% versus 25%; P<0.001) or GT/GG genotype (11% versus 0%; P=0.02), and low (44% versus 15%; P=0.04) or high (45% versus 17%; P<0.001) baseline viral load. For patients with 24-week or 48-week therapy, the SVR rate was significantly higher in those with IL28B rs8099917 TT genotype than those with GT/GG genotype (25% versus 0%; P<0.001; 60% versus 11%; P<0.001, respectively), but was comparable between those with low and high baseline viral loads (15% versus 17%, P=0.99; 44% versus 45%, P=0.99, respectively; Figure 3B).

Figure 3B also shows the stratified SVR rates by IL28B SNP genotypes, baseline viral load and treatment duration in non-RVR patients. Patients with 48-week therapy had significantly higher SVR rates than those with 24-week therapy for those with IL28B rs8099917 TT genotype and high baseline viral load (62% versus 23%; P<0.001), or with IL28B rs8099917 GT/GG genotype and low baseline viral load (33% versus 0%; P=0.02). In contrast, patients with 48-week therapy had a comparable SVR rate to patients with 24-week therapy for those with the IL28B rs8099917 TT genotype and a low baseline viral load (53% versus 40%, P=0.69), or with the IL28B rs8099917 GT/GG genotype and a high baseline viral load (6% versus 0%, P=0.99).
Discussion

Although the SVR rates in Western HCV-1 patients reach 54–63% with PEG-IFN and RBV therapy, the physicians can further improve the response rates by taking into account various viral and host factors [2–4]. Previous studies have demonstrated that baseline viral load, viral core gene substitutions and early viral kinetics are independent predictors of SVR [15,33]. HCV-1 patients with an RVR and low baseline viral load could receive a shorter duration of therapy without compromising the SVR rates, whereas those with slow responses to therapy should receive an extended duration of therapy [6,7,16,34]. The recent genome-wide association studies (GWAS) showed that favourable IL28B SNP genotypes (rs8099917 TT or rs12979860 CC) are highly associated with SVR in HCV-1 patients with 48 weeks of therapy. However, studies directly comparing 24 or 48 weeks of SOC in HCV-1 patients with different IL28B SNP genotype are still lacking.

Our data showed that in addition to baseline viral load, RVR and duration of therapy, the IL28B SNP genotype was an independent factor for SVR. In line with two recent reports, our results suggested that RVR, rather than IL28B rs8099917 TT genotype or low baseline viral load, was the best positive predictor for SVR [35,36]. Furthermore, the IL28B rs8099917 genotype and baseline viral load also independently affected the RVR rate, which was the key factor for SVR [6,7,22,23,36]. Patients with the IL28B rs8099917 TT genotype and low baseline load had an RVR rate of 89%; those with only one of these two favourable factors had RVR rates down to 40–43%; only 16% of those with neither of these two favourable factors achieved an RVR. In low baseline viral load patients who achieved an RVR, 48-week therapy did not provide

Figure 3. SVR rates stratified by IL28B rs8099917 genotypes (TT or GT/GG) and baseline viral load (low or high) in RVR patients and non-RVR patients with 24 or 48 weeks of therapy.

(A) Rapid virological response (RVR) patients and (B) non-RVR patients. The numerators at the base of the bar indicate the number of patients with sustained virological response (SVR); the denominators at the base of the bar indicate the total number of RVR and non-RVR patients.
a better SVR rate than 24-week therapy [6,7,16]. In contrast, 48-week therapy had a significantly higher SVR rate than 24-week therapy in patients with a high baseline viral load, or those with either the IL28B rs8099917 TT genotype or GT/GG genotype in the presence of an RVR. Although the IL28B SNP genotype and baseline viral load did not affect the SVR rates in RVR patients receiving 48-week therapy, these factors significantly affected the treatment responses in patients receiving 24-week therapy [22]. These findings implied that a shorter duration of therapy should be avoided in RVR patients who had IL28B rs8099917 GT/GG genotype or high baseline viral load.

Further analysis for RVR patients revealed that 194 of 662 (29.3%) patients with triple favourable factors (low baseline viral load, IL28B rs8099917 TT genotype and RVR) had a high SVR rate (95%) even with a shorter duration of therapy, which was in line with a recent report from Huang et al. [36]. Despite the presence of RVR and the IL28B rs8099917 TT genotype, a shorter duration of therapy significantly compromised 27% of SVR rate in patients with high baseline viral load. Furthermore, RVR patients with the IL28B rs8099917 GT/GG genotype should receive 48-week therapy to improve the SVR rates, regardless of the baseline viral load.

In non-RVR patients, a 48-week therapy had significantly higher SVR rates than a 24-week therapy, regardless of the IL28B SNP genotype and baseline viral load. These findings suggested that a 48-week treatment duration could improve the virological response in the presence of an unsatisfactory early viral decline. Of particular note, the IL28B rs8099917 genotype, rather than the baseline viral load, further affected the SVR rate in non-RVR patients receiving 48-week therapy. This was in sharp contrast with RVR patients receiving 48-week therapy, where the IL28B rs8099917 genotype did not affect SVR.

Further analysis for non-RVR patients showed that 48-week therapy had a significantly higher SVR rate than 24-week therapy for those with the IL28B rs8099917 TT genotype but a high baseline viral load, or those with the IL28B rs8099917 GT/GG genotype but a low baseline viral load, implying a shorter duration of therapy should be avoided in non-RVR patients bearing one additional unfavourable factor. The SVR rates were even worse for non-RVR patients bearing the IL28B rs8099917 GT/GG genotype and a high baseline viral load [36]. Patients with all the unfavourable factors could be advised to receive direct-acting antivirals in combination with PEG-IFN and RBV to improve the SVR rates. Although 48-week therapy had a higher SVR rate than 24-week therapy for non-RVR patients with the IL28B rs8099917 TT genotype and a low baseline viral load, it did not reach statistical significance because of small patient numbers (25 of 662 patients; 3.8%).

Although we demonstrated an individualized approach that can identify HCV-1 compliant patients who might benefit from 24 or 48-week therapy by IL28B SNP genotype, baseline viral load and RVR, some limitations existed [35]. First, all patients were East Asians, and the results should be validated in Western patients who have different RVR rates and IL28B SNP genotype distribution. Second, although the PPV for SVR in patients with triple favourable factors receiving 24 weeks of treatment was higher (95%) than that in those with dual favourable factors (low viral load plus RVR: 92%; IL28B rs8099917 TT genotype: 85%; IL28B rs8099917 TT genotype and low viral load: 90%), the overall patient coverage rate of patients with triple favourable factors was lower (29.3%) than that of those with dual favourable factors (32.1%, 50% and 33.1%, respectively). Adopting the IL28B rs8099917 TT genotype plus RVR predicting rule to truncate treatment duration might be feasible when patients are concerned about adverse events and increased medical cost. Third, the optimized duration of therapy for RVR patients with the IL28B rs8099917 GT/GG genotype and for non-RVR patients with the IL28B rs8099917 TT genotype and low baseline viral load remained unclear because of small patient numbers.

In summary, HCV-1 patients simultaneously bearing the IL28B rs8099917 TT genotype, low baseline viral load and RVR can receive 24-week combination therapy without compromising the SVR rate. Applying the truncated duration of therapy for super-responders might reduce the treatment-related adverse events and medical cost without compromising the therapeutic efficacy. In contrast, patients without these three favourable factors should at least receive 48-week combination therapy to secure the SVR rates.

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Disclosure statement

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