Background: Pegylated interferon and ribavirin for 72 weeks improve sustained virological response (SVR) in HCV genotype 1 (HCV-1) slow viral responders. Whether interleukin 28B (IL28B) single nucleotide polymorphism (SNP) genotypes and on-treatment viral responses can identify non-rapid virological response (NRVR) patients who benefit from 48 or 72 weeks of therapy remains unclear.

Methods: Treatment-naive HCV-1 patients who failed to achieve NRVR were randomly assigned to receive 48 ($n=168$) or 72 ($n=167$) weeks of therapy. Baseline factors and on-treatment virological responses at weeks 8 and 12 were evaluated for SVR in 289 compliant patients who received $\geq 80\%$ of drug dosages and treatment duration, and had end of follow-up viral response. The stratified SVR rates for independent factors were compared by treatment duration.

Results: Treatment duration, IL28B rs8099917 genotypes, cirrhosis, week-8 viral response (undetectable HCV RNA at treatment week 8) and complete early virological response (cEVR) predicted SVR. In week-8 viral response patients, the SVR rates of 72-week and 48-week treatment were similar (75–88%), regardless of IL28B SNP genotypes or cirrhosis. In non-week-8 viral response patients who achieved cEVR, the SVR rate of 72-week treatment was higher than that of 48-week treatment for non-cirrhotic patients, regardless of IL28B SNP genotypes (91–100% versus 13–44%; $P=0.001$).

Conclusions: Although IL28B SNP genotypes predict SVR, they play a minor role when on-treatment viral responses are taken into consideration. On-treatment viral responses at weeks 8 and 12 are the key determinants to decide the optimal treatment duration in HCV-1 patients without NRVR.

Introduction

Chronic HCV infection is the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma and liver transplantation [1]. Combination therapy of pegylated interferon (PEG-IFN) plus ribavirin (RBV) for 48 weeks is the standard of care to treat HCV genotype 1 (HCV-1) patients, with an overall sustained virological response (SVR) rate of 40–52% [2–5]. Among HCV-1 patients with low baseline viral load and rapid virological response (RVR), treatment for 24 weeks can achieve comparable SVR rates to treatment for 48 weeks [6–9]. By contrast, HCV-1 patients with slow viral response should be considered to receive extended treatment duration to improve the SVR rates [7,10–14]. Although using direct-acting antivirals, such as boceprevir or telaprevir, in combination with PEG-IFN and RBV further improves the SVR rates and has
become the new standard of care for treatment-naive and treatment-experienced HCV-1 patients, the added costs, increased treatment-related adverse events, and the possible emergence of viral resistance may preclude the unselected use of these agents [15–19].

Various baseline factors, including age, gender, body mass index, insulin resistance, hepatic steatosis/fibrosis, ethnicity, HCV viral load, RBV accumulative dosage, and on-treatment viral decline are associated with SVR [20]. In HCV-1 non-RVR patients, week-8 and week-12 viral responses may help determine 48 or 72 weeks of combination therapy [7,11–15]. Recently, the single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene (rs8099917 and rs12979860) are found to be associated with spontaneous or treatment-induced viral clearance, and early viral kinetics to treatment in HCV-1 patients [21–28]. The role of IL28B SNPs genotypes and viral decline beyond week 4 of treatment in identifying HCV-1 non-RVR patients who may benefit from standard or extended duration of therapy needs to be explored in more detail. In this study, we aimed to define the effect of IL28B SNPs genotypes on the SVR rate in these patients.

Methods

Patients

From 2007 to 2010, treatment-naive HCV-1 non-RVR patients, defined as those who failed to achieve undetectable HCV RNA at week 4 of treatment (Cobas TaqMan HCV Test version 2.0; Roche Diagnostics GmbH, Mannheim, Germany; detection limit of 15 IU/ml), were randomly assigned in a 1:1 ratio to receive 48 or 72 weeks of PEG-IFN-α2a (Pegasys; Hoffman-LaRoche, Basel, Switzerland; 180 μg/week) plus weight-based RBV (Copegus; Hoffman-LaRoche; 1,000 mg/day for <75 kg and 1,200 mg/day for ≥75 kg). Chronic HCV infection was defined as the presence of anti-HCV antibody (Abbott HCV EIA 3.0; Abbott Laboratories, Abbott Park, IL, USA) and serum HCV RNA >6 months. HCV genotype and subtype were determined by reverse hybridization assay (Inno-LiPA HCV II; Innogenetics, Ghent, Belgium).

Baseline haemogram, and demographic, biochemical, virological and histological data were evaluated before enrolment. All patients received liver biopsies before treatment and one independent pathologist staged the hepatic fibrosis by METAVIR score [29–31]. Human genomic DNA was extracted from peripheral blood mononuclear cells by QIAamp kits (Qiagen, Inc., Valencia, CA, USA). The IL28B SNP (rs8099917) genotypes (favourable homozygous TT genotype and unfavourable heterozygous GT and homozygous GG genotypes) were analysed by the ABI TaqMan allelic discrimination kit and ABI7900HT Sequence Detection System (Applied Biosystems, Life Technologies Corporation, Grand Island, NY, USA) because this SNP has been shown to be highly associated with treatment response [28]. Patients who met the exclusion criteria for treatment as previously described or were unwilling to provide written informed consent were excluded from the study [9].

Study design

This multicentre randomized study was conducted in six academic centres in Taiwan. The protocol was approved by the Ethical Committee of each participating centre and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Each non-RVR patient provided written informed consent before entering the study.

Serial serum HCV RNA levels were determined by Cobas TaqMan HCV assays at baseline, at weeks 4, 8, 12 and 24 of treatment, at the end-of-treatment and at week 24 after the end-of-treatment. RVR was defined as undetectable serum HCV RNA at week 4 of treatment [20]. Week-8 response (Wk-8R) was defined as undetectable serum HCV RNA at week 8 of treatment in the absence of RVR [7]. Complete early virological response (cEVR) was defined as undetectable serum HCV RNA at week 12 of treatment in the absence of RVR [7,9,12,20]. Patients who failed to achieve cEVR included those with partial early virological response (pEVR), defined as detectable viraemia at week 12 but ≥2 log reduction of serum HCV RNA from baseline to week 12 of therapy, and those without early virological response (EVR), defined as failure to achieve ≥2 log reduction of serum HCV RNA from baseline to week 12 of therapy [20]. The end-of-treatment virological response (ETVR) and SVR were defined as undetectable serum HCV RNA at the end-of-treatment and at week 24 after the end-of-treatment, respectively [20]. All patients who failed to achieve EVR were allowed to receive further treatment to 24 weeks to confirm non-response or slow response. All patients who remained with detectable HCV RNA or who had viral breakthrough at week 24 of treatment, and patients who were assigned to 72 weeks of treatment but had viral breakthrough at week 48 of treatment stopped further treatment. Patients with viral relapse, viral breakthrough and viral non-response were considered to have failed to achieve SVR. All patients received a monthly visit to assess the optimal drug dosage according to patients’ constitutional symptoms or laboratory abnormalities [9].

The SVR rates for all patients were determined by intention-to-treat (ITT) analysis. Because the SVR rate is highly associated with the dosage and duration of drug therapy, we evaluated the effects of baseline and on-treatment factors on the SVR rate in compliant patients who met the following criteria: completing the assigned
treatment duration, receiving ≥80% of both PEG IFN and RBV doses and ≥80% of treatment duration during the first 48 weeks (80/80/80 rule), and having end of follow-up data to assess SVR [32]. Although patients with viral non-response or viral breakthrough prematurely stopped treatment at week 24 or 48, they were still defined as compliant patients if they met the 80/80/80 rule during the first 24 or 48 weeks of treatment. The SVR rates for compliant patients were determined by per-protocol (PP) analysis. Significant hepatic fibrosis and cirrhosis were defined as a fibrosis stage of ≥F2 and F4 by METAVIR score, respectively [29,30].

Statistical analysis
All data were analysed by SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The estimated sample size was 167 patients in each group, based on the α and β error rates of 0.05 and 0.20, respectively, for a primary two-sided test, and 15% difference in SVR rates for both groups [7,10–12]. Patient characteristics were expressed as mean ±sd and percentage when appropriate. The deviation of IL28B rs8099917 genotypes from expectation was assessed by the Hardy–Weinberg equilibrium χ² test [33]. Univariate analyses of baseline factors and RBV accumulative dosage for SVR were performed by two-sample Student’s t-test and χ² with Fisher’s exact test [8,34]. Furthermore, we compared the predicted values of week-8 and week-12 viral responses for SVR. Factors with P-values of ≤0.10 by univariate analysis were entered into a multivariate analysis to find independent factors for SVR, which were expressed by odds ratios (ORs) with 95% CIs. The stratified SVR rates of significant baseline and on-treatment factors were compared in patients receiving 48 or 72 weeks of therapy by 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 761 HCV-1 patients receiving therapy, 426 RVR patients were excluded from the study. The IL28B rs8099917 genotype distribution in the 761 patients included TT genotype in 615 (80.8%), GT genotype in 139 (18.3%) and GG genotype in 7 (0.9%). Hardy–Weinberg disequilibrium analysis showed these patients were not deviated from expectation (χ²=0.09, P=0.99). The 335 non-RVR patients were randomly assigned to 48 (n=168) or 72 (n=167) weeks of therapy. Among them, 21 and 35 patients assigned to 48 and 72 weeks of treatment, respectively, prematurely stopped treatment due to viral non-response, viral breakthrough or adverse events. Finally, 329 of the 335 (98.2%) patients had end of follow-up data to assess SVR. The 289 (86.3%) compliant patients entered the PP analysis (Additional file 1). The baseline characteristics were comparable for the two treatment groups (Table 1).

Viral response rates to combination therapy
The on-treatment viral response rates by ITT or PP analysis were comparable for Wk-8R (48% versus 48%, P=0.99; 49% versus 47%, P=0.81), cEVR (78% versus 82%, P=0.41; 77% versus 81%, P=0.47), and ETVR (84% versus 85%, P=0.88; 85% versus 86%, P=0.74) between the 72- and 48-week treatment groups. However, patients with 72-week treatment had significantly higher SVR rates (65% versus 52%, P=0.03; 67% versus 54%, P=0.03) and lower relapse rates (23% versus 38%, P=0.007; 21% versus 38%, P=0.005) than those with 48-week treatment by ITT and PP analyses (Figure 1).

Baseline and on-treatment factors for SVR in compliant patients
By univariate analysis, treatment duration (P=0.03), age ≤60 years (P=0.004), absence of cirrhosis (P=0.001) and IL28B rs8099917 TT genotype (P<0.001) were baseline predictive factors for SVR (Table 2). In Wk-8R patients, the SVR rates were similar between the 72- and 48-week treatment groups (84% versus 85%, P=0.99). In non-Wk-8R patients, the SVR rate of the 72-week treatment group was higher than that of the 48-week treatment group (50% versus 26%, P=0.003). Considering the week-12 viral responses, the SVR rate of the 72-week treatment group was higher than that of the 48-week treatment group in cEVR patients (82% versus 62%, P<0.001). The SVR rates were comparable in 72- and 48-week treatment groups in pEVR patients (26% versus 17%, P=0.69) and non-EVR patients (0% versus 20%, P=0.16; Figure 2A). All Wk-8R patients achieved cEVR, and the SVR rates were similar between the 72- and 48-week treatment groups (84% versus 85%, P=0.99). Overall, 90 of 151 (60%) non-Wk-8R patients achieved cEVR, and the SVR rate of the 72-week treatment group was higher than that of 48-week treatment group (50% versus 26%, P<0.001). The SVR rates were comparable in the 72- and 48-week treatment groups in the remaining 61 (40%) non-Wk-8R and non-cEVR patients (15% versus 18%, P=0.99; Figure 2B).

Since week 8 and 12 viral responses can help discriminate the optimal treatment in HCV-1 non-RVR patients, the predictive models for SVR were built either by baseline factors or by incorporating on-treatment viral responses to baseline factors (Table 2). In the baseline model, 72-week treatment (OR 1.79 [95% CI 1.08, 2.98]; P=0.03), absence of cirrhosis (OR 2.61 [95% CI 1.50, 4.51]; P<0.001) and IL28B rs8099917 TT genotype (OR 2.60 [95% CI 1.54, 4.43]; P<0.001) were independent factors for SVR. In the combined model, presence of Wk-8R (OR 4.14 [95% CI 2.15, 8.00]; P<0.001) and cEVR (OR 6.28 [95% CI 2.72, 15.32]; P<0.001) were independent factors for SVR.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=335)</th>
<th>48-Week treatment (n=168)</th>
<th>72-Week treatment (n=167)</th>
<th>P-value</th>
<th>Compliant patients (n=289)*</th>
<th>48-Week treatment (n=145)</th>
<th>72-Week treatment (n=144)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years, n (%)</td>
<td>59 (35)</td>
<td>54 (32)</td>
<td>0.64</td>
<td></td>
<td>47 (32)</td>
<td>45 (31)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>95 (57)</td>
<td>91 (54)</td>
<td>0.74</td>
<td></td>
<td>84 (58)</td>
<td>82 (57)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 ±3.8</td>
<td>25.9 ±3.9</td>
<td>0.95</td>
<td></td>
<td>26.0 ±3.7</td>
<td>25.8 ±3.9</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>14.1 ±1.5</td>
<td>14.6 ±1.5</td>
<td>0.64</td>
<td></td>
<td>14.2 ±1.5</td>
<td>14.6 ±1.5</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>White blood cell, ×10³/l</td>
<td>5.2 ±1.6</td>
<td>5.3 ±1.8</td>
<td>0.23</td>
<td></td>
<td>5.2 ±1.6</td>
<td>5.4 ±1.9</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10³/l</td>
<td>158 ±51</td>
<td>161 ±55</td>
<td>0.17</td>
<td></td>
<td>162 ±52</td>
<td>165 ±53</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.1 ±0.3</td>
<td>4.3 ±0.4</td>
<td>0.11</td>
<td></td>
<td>4.2 ±0.3</td>
<td>4.3 ±0.4</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>1.0 ±0.5</td>
<td>1.0 ±0.4</td>
<td>0.19</td>
<td></td>
<td>1.0 ±0.4</td>
<td>1.1 ±0.4</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>ALT quotient &gt; ULN</td>
<td>3.5 ±2.3</td>
<td>3.6 ±2.6</td>
<td>0.44</td>
<td></td>
<td>3.6 ±2.2</td>
<td>3.7 ±2.8</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Baseline HCV RNA level, log₁₀ IU/ml</td>
<td>6.2 ±0.6</td>
<td>6.3 ±0.6</td>
<td>0.76</td>
<td></td>
<td>6.2 ±0.6</td>
<td>6.3 ±0.6</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Baseline HCV RNA level &gt; 800,000 IU/ml, n (%)</td>
<td>115 (68)</td>
<td>123 (74)</td>
<td>0.34</td>
<td></td>
<td>102 (70)</td>
<td>103 (72)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td>4 (2.4)</td>
<td>6 (3.6)</td>
<td>0.81</td>
<td></td>
<td>4 (2.7)</td>
<td>6 (4.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>a, n (%)</td>
<td>163 (97)</td>
<td>160 (95.8)</td>
<td>0.19</td>
<td></td>
<td>140 (96.6)</td>
<td>137 (95.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>b, n (%)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0.76</td>
<td></td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IL28B rs8099917 genotype</td>
<td>112 (66.7)</td>
<td>111 (66.5)</td>
<td>0.99</td>
<td></td>
<td>97 (66.9)</td>
<td>94 (65.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>TL, n (%)</td>
<td>53 (31.5)</td>
<td>53 (31.7)</td>
<td>0.45</td>
<td></td>
<td>46 (31.7)</td>
<td>47 (32.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>GT, n (%)</td>
<td>3 (1.8)</td>
<td>3 (1.8)</td>
<td>2.14</td>
<td></td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Significant hepatic fibrosis ≥F2, n (%)</td>
<td>145 (86)</td>
<td>139 (83)</td>
<td>0.45</td>
<td></td>
<td>123 (85)</td>
<td>118 (82)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis F4, n (%)</td>
<td>57 (34)</td>
<td>50 (30)</td>
<td>0.48</td>
<td></td>
<td>48 (33)</td>
<td>41 (28)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>RBV accumulative dosage</td>
<td>133 (79)</td>
<td>134 (80)</td>
<td>0.89</td>
<td></td>
<td>121 (83)</td>
<td>126 (88)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>≥13.3 mg/kg/day, n (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Data are mean ± sd unless indicated otherwise. Including 135 of 147 patients who completed 48 weeks of treatment, 10 of 14 patients with viral non-response in the 48-week arm, 118 of 132 patients who completed 72 weeks of treatment and 26 of 28 patients with viral non-response in the 72-week arm. All patients met the 80/80/80 rule and had end of follow-up data to determine sustained virological response (SVR). ALT, alanine aminotransferase; IL28B, interleukin 28B; RBV, ribavirin; ULN, upper limit of normal.

14.50]; P<0.001), 72-week treatment (OR 2.32 [95% CI 1.27, 4.24]; P<0.01), absence of cirrhosis (OR 2.29 [95% CI 1.20, 4.38]; P=0.01) and IL28B rs8099917 TT genotype (OR 1.87 [95% CI 1.01, 3.44]; P=0.04) were independent factors for SVR.

Stratified SVR rates in the baseline model
In non-cirrhotic patients with IL28B TT genotype, the SVR rate of 72-week treatment was higher than that of 48-week treatment (86% versus 69%, P=0.02). By contrast, the SVR rates of 72- and 48-week treatment were similar in cirrhotic patients with IL28B TT genotype (43% versus 45%, P=0.99) or with GT/GG genotype (44% versus 32%, P=0.51), and in non-cirrhotic patients with IL28B GT/GG genotype (53% versus 41%, P=0.44; Figure 3A).

Stratified SVR rates in the combined model
In Wk-8R patients, the SVR rates of 72- and 48-week treatment were similar in non-cirrhotic patients either with IL28B TT genotype (84% versus 88%, P=0.77) or with IL28B GT/GG genotype (88% versus 83%, P=0.99), and in cirrhotic patients either with IL28B TT genotype (86% versus 75%, P=0.99) or IL28B GT/GG genotype (80% versus 83%, P=0.99; Figure 3B). In non-Wk-8R patients who achieved cEVR, the SVR rates of 72- and 48-week treatment were similar in cirrhotic patients with IL28B TT genotype (43% versus 41%, P=1.00) or IL28B TT/GG genotype (43% versus 0%, P=0.08). However, the SVR rate of 72-week treatment was higher than that of 48-week treatment in non-cirrhotic patients with IL28B TT genotype (90% versus 38%, P<0.001) or IL28B TT/GG genotype (91% versus 13%, P=0.001; Figure 3C). In non Wk-8R patients who failed to achieve cEVR, the SVR rates of 72- and 48-week treatment were similar in non-cirrhotic patients either with IL28B TT genotype (60% versus 30%, P=0.33) or with IL28B GT/GG genotype (0% versus 11%, P=0.41), and in cirrhotic patients either with IL28B TT genotype (0% versus 11%, P=0.99) or IL28B GT/GG genotype (20% versus 17%, P=0.99; Figure 3D).

Discussion
Compared with HCV-1 RVR patients who can achieve high SVR rates with truncated duration...
### Table 2. Univariate and multivariate analyses of baseline and on-treatment factors predictive of sustained virological response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR (n=174)</td>
<td>Non-SVR (n=115)</td>
</tr>
<tr>
<td>Treatment duration (72 versus 48 weeks), n (%)</td>
<td>96/78 (67/54)</td>
<td>48/67 (33/46)</td>
</tr>
<tr>
<td>Age (≤60 versus &gt;60 years), n (%)</td>
<td>130/44 (66/37)</td>
<td>67/48 (34/73)</td>
</tr>
<tr>
<td>Gender (female versus male), n (%)</td>
<td>74/100 (60/60)</td>
<td>49/66 (40/40)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7 ±3.8</td>
<td>26.1 ±3.9</td>
</tr>
<tr>
<td>Platelet count, ×10^9/l</td>
<td>178 ±57</td>
<td>152 ±56</td>
</tr>
<tr>
<td>ALT quotient, ×ULN</td>
<td>3.8 ±2.8</td>
<td>3.6 ±2.0</td>
</tr>
<tr>
<td>Baseline HCV RNA level</td>
<td>51/123 (61/60)</td>
<td>33/82 (39/40)</td>
</tr>
<tr>
<td>(≤800,000 versus &gt;800,000 IU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV subtype (1a versus 1b versus 1a+1b), n (%)</td>
<td>8/165/1 (80/60/50)</td>
<td>2/112/1 (20/40/50)</td>
</tr>
<tr>
<td>IL28B rs8099917 genotype (TT versus GT/ GG), n (%)</td>
<td>131/43 (69/44)</td>
<td>60/55 (31/56)</td>
</tr>
<tr>
<td>Significant hepatic fibrosis (no versus yes), n (%)</td>
<td>30/144 (63/60)</td>
<td>18/97 (37/40)</td>
</tr>
<tr>
<td>Cirrhosis (no versus yes)</td>
<td>137/37 (69/42)</td>
<td>63/52 (31/58)</td>
</tr>
<tr>
<td>RBV accumulative dosage (≥133 versus &lt;133 mg/kg/day)</td>
<td>146/28 (58/67)</td>
<td>101/14 (41/33)</td>
</tr>
<tr>
<td>Wk-8R (yes versus no)</td>
<td>117/57 (85/38)</td>
<td>21/94 (15/62)</td>
</tr>
<tr>
<td>cEVR (yes versus no)</td>
<td>164/10 (72/16)</td>
<td>64/51 (28/84)</td>
</tr>
</tbody>
</table>

*Baseline factors. *Baseline plus on-treatment factors (baseline factors with a P-value ≤0.10 by univariate analysis entered into multivariate logistic regression analysis).

Values in parentheses indicate the rates of index responses. ALT, alanine aminotransferase; cEVR, complete early virological response; IL28B, interleukin 28B; OR, odds ratio; RBV, ribavirin; SVR, sustained virological response; ULN, upper limit of normal; Wk-8R, week 8 response.

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of therapy, the SVR rate is far from satisfactory in HCV-1 non-RVR patients [13]. In-line with previous reports, the SVR rate of 72-week treatment was significantly higher than that of 48-week treatment for all compliant HCV-1 non-RVR patients because of the lower relapse rate in the 72-week treatment group [10,12]. Furthermore, the premature discontinuation rates were similar between the 72-week and 48-week treatment groups, suggesting extended treatment was safe for such patients [7,10–13]. However, the additional medical expenses and decreased quality of life may limit the unrestricted use of prolonged therapy for these patients, and prompt us to investigate the individualized therapy by incorporating various host and viral factors.

The utility of EVR for HCV-1 non-RVR patients has been improved by distinguishing patients with cEVR, pEVR and non-EVR. Although the recent EASL guidelines recommended that cEVR and pEVR patients should receive 48 and 72 weeks of therapy to ensure the SVR rate, two studies found that the SVR rate of 72-week treatment was not significantly higher that of 48-week treatment for patients with cEVR or pEVR [10,12,35]. Our study demonstrated that the SVR rate of 72-week treatment was significantly higher than that of 48-week treatment for cEVR patients, whereas SVR rates were similar for pEVR and non-EVR patients receiving 72-week or 48-week treatment. This discrepancy could be reasoned by differences in study design, assigned regimens, definition of subgroups, and, most importantly, limited case number in subgroups of our study [13]. When the week-8 viral responses were taken into consideration, our data clearly showed that the Wk-8Rs help identify the optimal treatment duration for cEVR patients. However, extending the treatment duration did not benefit non-Wk-8R and non-cEVR patients. These data are in line with the report by Mangia et al. [7], demonstrating that 48-week treatment is sufficient for non-RVR patients who first achieve undetectable HCV RNA at week 8 of treatment, and 72-week treatment should be adopted for those who first achieve undetectable HCV RNA at week-12 of treatment. Testing Wk-8Rs would be more helpful to earlier identify the optimal treatment duration for HCV-1 non-RVR patients.

Similar to previous reports, we found that favourable IL28B SNP genotype, age ≤60 years and non-cirrhosis were associated with SVR [2–4,9,21–28,36–38]. Furthermore, we found that weight-based RBV accumulative dosage at a cutoff level of 13.3 mg/kg/day did not
affect the SVR rates [13,34]. Although IL28B SNP genotype and cirrhosis were highly associated with SVR in the baseline model, the effects decreased when the on-treatment viral responses at weeks 8 and 12 were taken into consideration in the combined model, implying that on-treatment viral factors may potentially be more important to predict SVR than the two baseline factors.

We further compared the stratified SVR rates in both models to help practicing physicians determine the optimal treatment duration. Despite the beneficial
effect that extending the treatment duration was demonstrated for non-cirrhotic IL28B TT genotype patients in the baseline model, the improved SVR rate was only observed in non-Wk-8R/cEVR patients (100% versus 44%), rather than in Wk-8R patients (88% versus 84%) or in non-Wk-8R/non-cEVR patients (60% versus 30%), in the combined model. By contrast, the improved SVR rate of extending the treatment duration was observed in non-cirrhotic IL28B GT/GG genotype patients with non-Wk-8R/cEVR in the combined model (91% versus 13%), whereas it did not differ in the baseline model (53% versus 41%). Although extending the treatment duration did not improve the SVR rates in cirrhotic patients with either TT or GT/GG genotype, the SVR rates were much higher in Wk-8R (75–86%) than in non-Wk-8R (0–43%) patients with standard or extended treatment duration. These findings had three clinical implications for HCV-1 non-RVR patients: the on-treatment week 8 and 12 viral responses were the key determinants to help decision making [7,13,39], Wk-8R patients could keep high SVR rates by standard treatment duration, regardless of the IL28B SNP genotype or the status of cirrhosis [7,13] and the non-Wk-8R/cEVR patients who were non-cirrhotic might still have high SVR rates by extending the treatment duration, while the non-Wk-8R/non-cEVR patients had relatively low SVR rates despite of extended treatment duration. Thus physicians may consider triple combination therapy with direct-acting antivirals for non-Wk-8R/cEVR patients who were cirrhotic and for non-Wk8R/non-cEVR patients to increase the SVR rate [15–19].

Although we demonstrated an individualized approach to identify compliant HCV-1 non-RVR patients who may benefit from standard or extended treatment duration, some limitations existed. First, all patients were East Asian, and the results should be validated in Western patients with different IL28B SNP genotype distribution. Second, the optimal treatment duration for IL28B TT genotype non-cirrhotic patients who failed to achieve Wk-8R and cEVR needed to be confirmed because the patient number in this subgroup was relatively small.

In summary, compliant HCV-1 non-RVR patients should receive 48-week therapy if they achieve Wk-8R. Non-Wk-8R/cEVR patients who were non-cirrhotic should receive 72-week therapy, regardless of IL28B SNP genotypes.

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Disclosure statement

J-HK is a consultant for Abbott, Bristol–Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche, and is on the speaker’s bureau for Abbott, Roche, Bayer, Bristol–Myers Squibb, GlaxoSmithKline and Novartis. D-SC is a consultant for Novartis and GlaxoSmithKline. P-JC is a consultant for Novartis and Roche. All other authors declare no competing interests.

Additional file

Additional file 1: Supplementary Figure 1, a flow diagram of the study, can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2369_Liu_Add_file1.pdf

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