Peginterferon alfa-2a plus Weight-Based or Flat-Dose Ribavirin for Treatment-Naïve Hepatitis C Virus Genotype 2 Rapid Responders: A Randomized Trial

Chen-Hua Liu1,4, Chung-Feng Huang5,6,7, Chun-Jen Liu1,3, Chia-Yen Daï5,6,8, Jee-Fu Huang5,6,8, Jou-Wei Lin4, Cheng-Chao Liang9, Sheng-Shun Yang10, Chih-Lin Lin11, Tung-Hung Su1,3, Hung-Chih Yang1,2,3,12, Pei-Jer Chen1,3,1, Ding-Shinn Chen1,3,3,3, Wan-Long Chuang5,6,8, Jia-Horng Kao1,3 & Ming-Lung Yu5,6,8

The impact of ribavirin (RBV) dosage on sustained virologic response (SVR) rates remains elusive in hepatitis C virus genotype 2 (HCV-2) rapid responders receiving 16 weeks of peginterferon (Peg-IFN) plus RBV. Treatment-naïve HCV-2 patients with rapid virologic response (RVR) received Peg-IFN alfa-2a 180 μg/week plus weight-based RBV (1,000 or 1,200 mg/day; cut-off body weight: 75 kg) for 6 weeks, and then randomly received Peg-IFN alfa-2a 180 μg/week plus weight-based (1,000 or 1,200 mg/day; n = 247) or flat-dose (800 mg/day; n = 246) RBV for additional 10 weeks. The primary endpoint was SVR24. Patients receiving weight-based and flat-dose RBV therapies had comparable SVR24 rates (93.5% versus 91.9%, P = 0.49). The risk differences (RDs) of SVR24 receiving weight-based and flat-dose RBV arms were 7.1% [95% CI: 0.7% to 13.6%] in males, and −5.8% [95% CI: −12.1% to 0.5%] in females (interaction P = 0.01). The SVR24 rate was higher in males receiving ≥13 mg/kg/day than those receiving <13 mg/kg/day (96.3% versus 85.1%, P = 0.001). In conclusion, Peg-IFN alfa-2a plus weight-based or flat-dose RBV for 16 weeks provides comparable SVR24 rates in treatment-naïve HCV-2 rapid responders. However, males should receive weight-based RBV to achieve a high SVR24 rate.

Hepatitis C virus (HCV) infection remains the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC) and liver transplantation1. While HCV genotype 2 (HCV-2) infection is
relatively uncommon in North America and West Europe (except for Northern Italy), it is common in East Asia. In the era of peginterferon (Peg-IFN) plus ribavirin (RBV) therapy, the SVR rates in patients with HCV-2/3 infection are higher (75–95% versus 39–79%) than those in patients with HCV-1/4 infection. Although the safety and efficacy of the recently introduced sofosbuvir-based therapies are excellent for HCV-2 patients, the treatment costs and the drug availability preclude the unselected use of these agents.

In HCV-2 patients who receive Peg-IFN plus RBV and who achieve rapid virologic response (RVR), the SVR rates are comparable if they receive 12–16 weeks or 24 weeks of therapy. The SVR rates are also similar in these patients with different interleukin-28B (IL-28B) genotypes. However, the impact of weight-based (1,000 or 1,200 mg/day) or flat-dose (800 mg/day) RBV on the SVR rates in HCV-2 patients achieving RVR remains controversial. For HCV-2 patients achieving RVR after 6 weeks of induction therapy by Peg-IFN alfa-2a plus weight-based RBV, we aimed to compare the efficacy of additional 10 weeks of therapy by Peg-IFN alfa-2a plus weight-based or flat-dose RBV, and to evaluate the factors associated with anti-viral responses.

Results

Patient Characteristics. Among 495 patients who achieved RVR after 6 weeks of Peg-IFN alfa-2a plus weight-based RBV induction therapy, 493 were allocated at week 6 of treatment to receive Peg-IFN alfa-2a plus weight-based (n = 247) or flat-dosed (n = 246) RBV for additional 10 weeks. Two hundred and forty (97.2%) patients and 240 (97.6%) patients in weight-based and flat-dose RBV arms completed the assigned treatment, respectively. In addition, 234 (94.7%) patients and 230 (93.5%) patients in these two arms completed off-therapy follow-up to assess SVR24 (Fig. 1). The baseline patient characteristics were comparable between the two arms (Table 1). Most patients had baseline viral load of < 800,000 IU/mL (79%) and favorable interleukin-28B (IL-28B) rs8099917 genotype (87%), and were infected with 2a subtype (75%). With regard to aspartate aminotransferase (AST) to platelet ratio index (APRI) score, 23.7% of the patients had a score of > 2.00.

Efficacy. The end-of-treatment virologic response (ETVR) (100.0% versus 99.6%, risk difference (RD): 0.4% [95% confidence interval (CI): −0.7% to 1.5%]; P = 0.50) and the SVR24 rates (93.5% versus 91.9%, RD: 1.7% [95% CI: −2.9% to 6.2%]; P = 0.49) were comparable between the weight-based and flat-dose RBV arms (Table 2).

We performed the sensitivity analyses to assess the impact of 6 and 9 patients who failed to achieve SVR24 due to undetermined reason in weight-based and flat-dose RBV arms (Table 2). As a best-case scenario, we assumed that the 6 patients in weight-based RBV arm who achieved SVR24 and the 9 patients in flat-dose RBV arm who failed to achieve SVR24. As a worst-case scenario, we assumed that the 6 patients in weight-based RBV arm who achieved SVR24 and the 9 patients in flat-dose RBV arm who achieved SVR24. Results from the best-case scenario (96.0% versus 91.9%, RD: 4.1% [95% CI: −0.1% to 8.3%]; P = 0.10) and the worst-case scenario (93.5% versus 95.5%, RD: −2.0% [95% CI: −6.0% to 2.0%]; P = 0.43) were consistent with the primary endpoint.

Subgroup Analyses for Prespecified Factors. Differences of the SVR24 rates between weight-based and flat-dose RBV arms did not vary by baseline viral load (interaction P = 0.33), subgenotype (interaction P = 0.61), IL-28B rs8099917 genotype (interaction P = 0.99), age (interaction P = 0.18), weight (interaction P = 0.71), APRI score (interaction P = 0.11), RBV dosage (interaction P = 0.88) or 80/80/80 rule (interaction P = 0.64) (Table 3). Compared with females (91.3% versus 97.1%, RD: −5.8% [95% CI: −12.1% to 0.5%]), males in weight-based RBV arm achieved a greater SVR24 rate than those in flat-dose RBV arm (95.1% versus 88.0%, RD: 7.1% [95% CI: 0.7% to 13.6%]; interaction P = 0.01). We further examined the daily RBV exposure in males and females receiving weight-based and flat-dose RBV. Compared to patients in flat-dose RBV arm, those in weight-based RBV arm received a greater RBV dosage (15.4 mg/kg/day [SD, 2.6] versus 12.9 mg/kg/day [SD, 2.1], P < 0.001), regardless of males (14.4 mg/kg/day [SD, 1.9] versus 12.4 mg/kg/day [SD, 2.0], P < 0.001) or females (16.8 mg/kg/day [SD, 2.9] versus 13.6 mg/kg/day [SD, 2.1], P < 0.001). Patients receiving RBV at a dosage of ≥ 13 mg/kg/day had a greater SVR24 rate than those receiving RBV at a dosage of < 13 mg/kg/day (95.7% versus 87.1%; P = 0.001). While the SVR24 rates were similar in females receiving RBV at a dosage of ≥ 13 and < 13 mg/kg/day (94.3% versus 93.9%, P = 0.99), the SVR24 rate in males receiving RBV at a dosage of ≥ 13 mg/kg/day was greater than those receiving RBV at a dosage of < 13 mg/kg/day (97.0% versus 84.3%, P < 0.001) (Table 4).

Safety. The constitutional and laboratory adverse events (AEs) were similar between two arms (Table 5). Two patients in weight-based RBV arm and one in flat-dose RBV arm had serious AEs during treatment (0.8% versus 0.4%, RD: 0.4% [95% CI: −1.0% to 1.8%]). The AE-related withdrawal rates were 2.8% in weight-based RBV arm and 2.4% in flat-dose RBV arm (RD: 0.4% [95% CI: −2.4% to 3.2%]). During the first 6 weeks of treatment, 6.1% and 6.5% of the patients receiving weight-based and flat-dose RBV had anemia (RD: −0.4% [95% CI: −3.9% to 4.7%]). Furthermore, 20.2% and 15.0% of the patients receiving weight-based and flat-dose RBV had anemia (RD: 5.2% [95% CI: −1.5% to 11.9%]) between weeks 6 and 16 of treatment.
Discussion

Our study demonstrated that Peg-IFN alfa-2a plus weight-based or flat-dose RBV for 16 week provided high SVR rates in HCV-2 rapid responders. The SVR rates in our patients (91.9% to 93.5%) were greater than those in HCV-2 slow responders receiving 24–48 weeks of Peg-IFN plus RBV therapy (46.2% to 52.6% for 24 weeks; 71.4% for 36 weeks; 68.4% to 77.8% for 48 weeks), suggesting that the early viral kinetics play an important role in determining the anti-viral responses in these patients. Furthermore we also showed that treatment with Peg-IFN alfa-2a plus weight-based RBV provided a comparable SVR rate (93.5% versus 91.9%) and treatment-related withdrawal rate (2.8% versus 2.4%) to treatment with Peg-IFN alfa-2a plus flat-dose RBV, suggesting HCV-2 rapid responders may receive Peg-IFN plus flat-dose RBV for 16 weeks to achieve high a SVR rate and a low AE rate. While the SVR rate was greater in males receiving Peg-IFN alfa-2a plus weight-based RBV than that in males receiving Peg-IFN alfa-2a plus flat-dose RBV (95.1% versus 88.0%).

Although the SVR rates between weight-based and flat-dose RBV arms were similar stratified by baseline viral load, subgenotype, IL-28B genotype, age, weight, APRI score, RBV dosage or 80/80/80 rule, males in weight-based RBV arm achieved a significant greater SVR rate than those in flat-based RBV arm. We further examined the possible factors for the gender effects. The mean dosage of RBV in weight-based RBV arm was significantly greater than flat-dose RBV arm, regardless of gender. When we stratified the RBV dosage at a cut-off value of 13 mg/kg/day, we revealed that males with a RBV dosage of ≥13 mg/kg/day had a greater SVR rate than those with a dosage of <13 mg/kg/day, but the SVR rates in females were similar whether they received a RBV dosage of ≥13 mg/kg/day or not. Manns et al.
demonstrated that the SVR24 rate tended to increase in HCV-infected patients if they received a RBV dosage of ≥13 mg/kg/day. Our study implied that although males who achieved RVR after induction therapy with Peg-IFN alfa-2a plus weight-based RBV, a sufficiently high dosage of RBV (≥13 mg/kg/day) should be maintained to secure a high SVR rate if they received a truncated treatment duration for 16 weeks. In females who achieved RVR after Peg-IFN alfa-2a plus weight-based RBV induction therapy, the SVR24 rate tended to decrease.

### Table 1. Baseline Patient Characteristics

| Characteristics | Peg-IFN plus weight-based RBV, N = 247 | Peg-IFN plus flat-dose RBV, N = 246 |
|-----------------|----------------------------------------|-------------------------------------|
| Mean age (SD), y | 55 (11)                                | 56 (11)                             |
| Age >50 y       | 163 (66)                                | 168 (68)                            |
| Male            | 143 (58)                                | 142 (58)                            |
| Mean weight (SD), kg | 66 (11)                                | 65 (10)                             |
| Male            | 70 (8)                                  | 69 (10)                             |
| Female          | 60 (9)                                  | 61 (8)                              |
| Weight ≥75 kg   | 55 (22.3)                               | 52 (21.1)                           |
| Mean BMI (SD), kg/m² | 25.2 (3.3)                             | 25.3 (3.4)                          |
| Mean hemoglobin level (SD), g/dL | 14.4 (1.4)                             | 14.2 (1.4)                          |
| Mean white cell count (SD), 10⁶ cells/L | 3.1 (1.1)                               | 3.0 (1.1)                           |
| Mean neutrophil count (SD), 10⁹ cells/L | 176 (48)                               | 173 (50)                            |
| Mean platelet count (SD), 10¹² cells/L | 2.2 (1.4)                               | 2.3 (1.3)                           |
| Mean albumin level (SD), g/dL | 4.2 (0.4)                               | 4.2 (0.9)                           |
| Mean total bilirubin level (SD), mg/dL | 0.9 (0.3)                              | 1 (0.4)                             |
| Mean AST quotient (SD), ULN | 2.2 (1.4)                              | 2.3 (1.3)                           |
| Mean ALT quotient (SD), ULN | 3.4 (2.4)                              | 3.4 (2.2)                           |
| Mean APRI score (SD) | 1.4 (1.2)                              | 1.5 (1.2)                           |
| APRI score ≤1.50 | 158 (64.0)                              | 149 (60.6)                          |
| 1.51–2.0        | 34 (13.7)                               | 35 (14.2)                           |
| >2.00           | 55 (22.3)                               | 62 (25.2)                           |
| Mean HCV RNA level (SD), log₁₀ IU/mL | 5.4 (0.8)                              | 5.3 (0.8)                           |
| HCV RNA level ≤800,000 IU/mL | 195 (79)                               | 193 (78)                            |
| >800,000 IU/mL  | 52 (21)                                 | 53 (22)                             |
| Subgenotype     |                                        |                                     |
| 2a              | 185 (75)                                | 185 (75)                            |
| 2b              | 52 (21)                                 | 46 (19)                             |
| 2a + 2b         | 10 (4)                                  | 15 (6)                              |
| IL-28B rs8099917 genotype† |                                        |                                     |
| TT              | 203 (86)                                | 202 (88)                            |
| GT and GG       | 32 (14)                                 | 28 (12)                             |

*Values are numbers (percentages) unless otherwise indicated. †Available number of patients (%) for analysis: 235 (95%) and 230 (93%) in weight-based RBV and flat-dose RBV arms, respectively.*
flat-dose RBV therapy may be preferred at treatment weeks 6–16 because it did not compromise the SVR24 rate and may lessen the severity of RBV-induced anemia.

With regard to safety, treatment by Peg-IFN alfa-2a plus RBV for 16 weeks showed low rates of serious AE and treatment withdrawal in weight-based and flat-dose RBV arms. Except for the tendency of clinically significant anemia at treatment weeks 6–16 in weight-based RBV arm, the constitutional symptoms and the other laboratory abnormalities of interest were comparable between the two arms. However, the proportions of severe anemia (Hb < 8.5 g/dL) which warranted temporary RBV discontinuation were low (6.9% and 6.1%) in weight-based and flat-dose RBV arms, respectively, implying that by careful monitoring the on-treatment hemoglobin levels and titrating the RBV dosages, most patients receiving weight-based or flat-dose RBV may safely complete treatment.

Our study had several limitations. First, our patients were East Asians, and the results should be validated in patients of different ancestry. Second, with the introduction of sofosbuvir-base therapies which confers excellent treatment responses, Peg-IFN plus RBV therapy may not be listed in the first-line therapy in Western countries. Despite the potentially higher on-treatment AE rates by Peg-IFN plus RBV therapy, our study also showed that HCV-2 rapid responders may also achieve high SVR rates by 16 weeks of therapy. The use of our strategies may provide a practical guide of IFN-eligible HCV-2 patients in resource-limited countries for sofosbuvir-based therapy.

In conclusion, Peg-IFN alfa-2a plus weight-based or flat-dose RBV for 16 weeks provides comparable SVR rates for treatment-naïve HCV-2 patients with RVR. However, males should receive Peg-IFN alfa-2a plus weight-based RBV to provide a high SVR rate.

### Materials and Methods

**Patients.** Treatment-naïve Taiwanese HCV-2 patients who were old than ≥18 years who had serum alanine aminotransferase (ALT) level ≥ upper limit of normal (ULN) were consecutively enrolled between 2007 and 2013 in the Tailored Regimens of Peginterferon alfa-2a and Ribavirin for Genotype 2 Chronic Hepatitis C Patients (TARGET-2) trial. Chronic HCV infection was defined as documentation of anti-HCV antibody (Abbott HCV EIA 3.0, Abbott Laboratories, Abbott Park, Illinois, USA) and HCV RNA (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, limit of detection: 15IUL/mL) for ≥6 months. The HCV genotyping was tested by reverse hybridization assay (Versant HCV Genotype 2.0 assay, Siemens Healthcare Diagnostics, Illinois, USA).

The exclusion criteria of the study were as follows: hemoglobin levels <13 g/dL for men or <12 g/dL for women, neutrophil count <1.5 × 10^9 cells/L, platelet count <90 × 10^9 cells/L, hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection, HCV infection other than genotype 2, alcohol consumption >20 g/day, serum albumin level <35 g/L, serum bilirubin level ≥1.5 times ULN, serum AST or ALT level ≥10 times ULN, serum creatinine level ≥1.5 times ULN, Child-Puge grade B or C

| Variable | Peg-IFN plus weight-based RBV, n/N (%) | Peg-IFN plus flat-dose RBV, n/N (%) | RD (95% CI) | P value*
|---|---|---|---|---
| On-treatment virologic response | | | | |
| ETVR | 247/247 (100.0) | 245/246 (99.6) | 0.4 (−0.7 to 1.5) | 0.50
| Virologic outcome | | | | |
| SVR24† | 231/247 (93.5) | 226/246 (91.9) | 1.7 (−2.9 to 6.2) | 0.49
| Non-SVR24 | 16/247 (6.5) | 20/246 (8.1) | | |
| Relapse | 10/247 (4.0) | 10/246 (4.1) | | |
| Null-response | 0 | 0 | | |
| Viral breakthrough‡ | 0 | 1/246 (0.4) | | |
| Undetermined§ | 6/247 (2.4) | 9/246 (3.7) | | |

Table 2. On-treatment and Off-therapy Virologic Responses. Peg-IFN: peginterferon, RBV: ribavirin, RD: risk reduction, EVR: early virologic response, ETVR: end-of-treatment virologic response, SVR: sustained virologic response, CI: confidence interval. *P values were obtained by Wald asymptotic test. †Patients who were lost to 24-week follow-up, were null-responsive to treatment, or had viral breakthrough or relapsed after treatment were considered failure to achieve SVR24. ‡One patient in flat-dose RBV arm had viral breakthrough at week 16 of treatment. §All patients lost to 24-week off-therapy follow-up, and all had undetectable HCV RNA level at the time of treatment discontinuation. Weight-based RBV arm: 5 completed 16 weeks of treatment, and 1 prematurely discontinued treatment at week 8 due to serious adverse event. Flat-dose RBV arm: 8 completed 16 weeks of treatment, and 1 prematurely discontinued treatment at week 12 due to adverse event.
Table 3. Subgroup Analyses of Prespecified Factors for SVR24. Peg-IFN: peginterferon, RBV: ribavirin, RD: risk reduction, CI: confidence interval, IL: interleukin, BMI: body mass index, APRI: aspartate aminotransferase to platelet ratio index, RBV: ribavirin. *The interaction for the prespecified factors was compared by stratified Mantel-Haenszel test. †Available number of patients (%) for analysis: 235 (95%) and 230 (93%) in weight-based RBV and flat-dose RBV arms, respectively. ‡The daily RBV dosage was calculated by total exposure of ribavirin divided by the actual duration of treatment and the baseline body weight. §Denotes patients who received \( \geq 80\% \) of both Peg-IFN alfa-2a and RBV doses for \( \geq 80\% \) of the expected duration of therapy.

| Variable                          | Peg-IFN plus weight-based RBV, n/N (%) | Peg-IFN plus flat-dose RBV, n/N (%) | RD (95% CI) | P value for interaction* |
|----------------------------------|---------------------------------------|-------------------------------------|-------------|--------------------------|
| Baseline viral load             |                                       |                                     |             | 0.33                     |
| \( \leq 800,000\)IU/mL          | 191/195 (97.9)                        | 185/193 (95.9)                     | 2.1 (−1.4 to 5.5) |             |
| \( > 800,000\)IU/mL            | 40/52 (76.9)                          | 41/53 (77.4)                       | 0.4 (−16.5 to 15.6) |             |
| Subgenotype                     |                                       |                                     |             | 0.61                     |
| 2a                               | 173/185 (93.5)                        | 170/185 (91.9)                     | 1.6 (−3.7 to 6.9) |             |
| 2b                               | 49/52 (94.2)                          | 42/46 (91.3)                       | 2.9 (−7.4 to 13.2) |             |
| 2a + 2b                          | 9/10 (90.0)                           | 14/15 (93.3)                       | 3.3 (−19.1 to 25.8) |             |
| IL-28B rs8099917 genotype†      |                                       |                                     |             | 0.99                     |
| TT                               | 189/203 (93.1)                        | 183/202 (90.6)                     | 2.5 (−2.8 to 7.8) |             |
| GT and GG                        | 30/32 (93.8)                          | 28/28 (100)                        | −6.3 (−16.5 to 3.9) |             |
| Age                              |                                       |                                     |             | 0.18                     |
| \( \leq 50\) y                  | 79/84 (94.0)                          | 68/78 (87.2)                       | 6.9 (−2.1 to 15.9) |             |
| \( > 50\) y                     | 152/163 (93.3)                        | 158/168 (94.0)                     | −0.8 (−6.1 to 4.5) |             |
| Sex                              |                                       |                                     |             | 0.01                     |
| Female                           | 95/104 (91.3)                         | 101/104 (97.1)                     | −5.8 (−12.1 to 0.5) |             |
| Male                             | 136/143 (95.1)                        | 125/142 (88.0)                     | 7.1 (0.7 to 13.6)  |             |
| Weight                           |                                       |                                     |             | 0.71                     |
| \( < 75\) kg                    | 181/192 (94.3)                        | 181/194 (93.3)                     | 1.0 (−3.8 to 5.8)  |             |
| \( \geq 75\) kg                 | 50/55 (90.9)                          | 45/52 (86.5)                       | 4.4 (−7.6 to 16.4) |             |
| APRI score                       |                                       |                                     |             | 0.11                     |
| \( \leq 1.50\)                  | 145/158 (91.8)                        | 136/149 (91.3)                     | 0.5 (−5.7 to 6.7)  |             |
| 1.51–2.00                       | 31/34 (91.8)                          | 34/35 (97.1)                       | −6.0 (−17.0 to 5.1) |             |
| \( > 2.00\)                     | 55/55 (100)                           | 56/62 (90.3)                       | 9.7 (−1.8 to 17.6) |             |
| RBV dosage‡                      |                                       |                                     |             | 0.88                     |
| \( < 13\) mg/kg/day             | 34/40 (85.0)                          | 114/130 (87.7)                     | −2.7 (−15.1 to 9.7) |             |
| \( \geq 13\) mg/kg/day          | 197/207 (95.2)                        | 112/116 (96.6)                     | −1.4 (−5.8 to 3.0)  |             |
| Meet 80/80/80 rule§              |                                       |                                     |             | 0.64                     |
| Yes                              | 203/216 (94.0)                        | 204/222 (91.9)                     | 2.1 (−2.7 to 6.9)  |             |
| No                               | 28/31 (90.3)                          | 22/24 (91.7)                       | −1.3 (−16.5 to 13.8) |             |

cirrhosis, history of autoimmune liver diseases or neoplastic diseases, concurrent immunosuppressive therapy, pregnancy, poorly controlled systemic illness or unwilling to receive birth control during the study period.

The study was approved by Taiwan Joint Institutional Review Board. All study procedures were conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Patients who were willing to join the study provided written informed consent before enrollment.

**Study Design.** This was a multicenter randomized controlled trial. All patients who were eligible to participate in this trial received induction therapy of Peg-IFN alfa-2a 180μg/week (Pegasys, Hoffman-LaRoche, Basel, Switzerland) plus weight-based RBV 1,000 or 1,200 mg/day (Copegus, Hoffman-LaRoche, Basel, Switzerland; cut-off body weight: 75kg) for 6 weeks. The viral responses at week 4 of treatment were evaluated for all patients. At week 6 of treatment, patients who achieved rapid virologic response (RVR), defined as undetectable serum HCV RNA at week 4 of treatment, were
randomly assigned as 1:1 ratio to receive Peg-IFN alfa-2a 180 μg/week plus weight-based (1,000 or 1,200 mg/day) or flat-dose (800 mg/day) RBV for additional 10 weeks (Fig. 2). Randomization code was computer-generated in blocks of 4 and secured by an independent assistant. In addition, all patients were centrally allocated to the assigned treatment. Baseline demographic data, hemoglobin level, neutrophil count, and platelet count, serum albumin, serum bilirubin, serum AST, serum ALT, serum creatinine, anti-HCV, HBsAg, anti-HIV, HCV RNA, HCV genotype, and IL-28B rs8099917 genotypes (ABI TaqMan allelic discrimination kit and ABI7900HT Sequence Detection System, Applied Biosystems, Life Technologies Corporation, Grand Island, New York, USA) were evaluated. The hepatic fibrosis was staged by APRI 30. Low baseline viral load was defined as a level of <800,000 IU/mL, whereas high baseline viral load was defined as a level of ≥800,000 IU/mL. IL-28B rs8099917 TT genotype was defined as favorable genotype, and GT/GG genotype was defined as unfavorable genotype, respectively 31–33. An APRI score of >1.50 and >2.00 denoted significant hepatic fibrosis (≥F2 by Metavir score) and cirrhosis (F4 by Metavir score), respectively 34.

Efficacy. All patients received treatment for 16 weeks and the off-therapy follow-up for 24 weeks. Serum HCV RNA levels were assessed at weeks 4 and 16 of treatment, and at week 24 after the cessation of therapy. The ETVR and the SVR24 were defined as previously described 11. The ETVR was assessed for all patients who early discontinued treatment at the treatment discontinuation. The primary endpoint was SVR24, defined as undetectable serum HCV RNA 24 weeks after the cessation of therapy. Patients with viral breakthrough at the end-of-treatment were considered failure to achieve SVR24, regardless of the end of follow-up HCV RNA data. Patients who lacked the end of follow-up data to assess SVR24 or who relapsed after the cessation of treatment were also considered failure to achieve SVR24. Sensitivity analyses were done for the primary endpoint.

Safety. During the study period, the safety profiles were reported by a prespecified checklist to assess the severity and the causality of the AEs. The grades of all AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. If the patients had serious AEs, missed assess the severity and the causality of the AEs. The grades of all AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. If the patients had serious AEs, missed assess the severity and the causality of the AEs. The grades of all AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. If the patients had serious AEs, missed assess the severity and the causality of the AEs. The grades of all AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. If the patients had serious AEs, missed

### Table 4. Daily Ribavirin Dosage and the SVR24 Rates in Male and Female Patients.

| Gender | Ribavirin dosage | SVR24, n/N (%) | SVR24, n/N (%) | P value |
|--------|------------------|----------------|----------------|---------|
|        | <13 mg/kg/day    |                 | ≥13 mg/kg/day  |         |
| Female | 46/49 (93.9)     | 150/159 (94.3) | 0.99           |
| Male   | 102/121 (84.3)   | 159/164 (97.0) | <0.001         |
| Total  | 148/170 (87.1)   | 309/323 (95.7) | 0.001          |

Statistical Analyses. Analysis of the data was performed by Statistical Program for Social Sciences (SPSS 17.0; SPSS Inc., Chicago, Illinois, USA). Based on the assumption that the SVR24 rate was 86% for patients assigned to receive Peg-IFN plus flat-dose RBV, we estimated that 488 patients would provide 90% power to detect an absolute increase of 8% or more in SVR24 for patients assigned to receive Peg-IFN plus weight-based RBV (2-sided α = 0.05) 12,16. Values were expressed as mean (standard deviation, SD) or percentage when appropriate.

The on-treatment and off-therapy viral response rates between weight-based and flat-dose RBV arms were compared by RD. The P values for RD were assessed by the Wald asymptotic test. The subgroup analyses for the factors of interest to predict SVR24, including baseline viral load, HCV subgenotype, IL-28B rs8099917 genotype, age, sex, body weight, APRI score, RBV dosage, and 80/80/80 rule were compared by RD 17. The interactions between the prespecified factors and the treatment arms were evaluated by the stratified Mantel-Haenszel test. The dosage of RBV associated with SVR was compared by
| Parameter                                      | Peg-IFN plus weight-based RBV, N = 247 | Peg-IFN plus flat-dose RBV, N = 246 |
|-----------------------------------------------|---------------------------------------|-------------------------------------|
| Serious AEs                                   |                                       |                                     |
| All†                                          | 2 (0.8)                               | 1 (0.4)                             |
| Death                                         | 0 (0)                                 | 0 (0)                               |
| Treatment-related                             | 2 (0.8)                               | 1 (0.4)                             |
| Treatment withdrawal due to AEs               | 7 (2.8)                               | 6 (2.4)                             |
| Dose reduction to AEs                         |                                       |                                     |
| Peginterferon                                 | 38 (15.3)                             | 36 (14.6)                           |
| Ribavirin                                     | 59 (23.9)                             | 49 (19.9)                           |
| Constitutional AEs                            |                                       |                                     |
| Flu-like symptoms                             | 71 (28.7)                             | 69 (28.0)                           |
| Fatigue                                       | 145 (58.7)                            | 146 (59.3)                          |
| Headache                                      | 73 (29.6)                             | 70 (28.5)                           |
| Insomnia                                      | 90 (36.4)                             | 88 (35.8)                           |
| Irritability                                  | 24 (9.7)                              | 25 (10.2)                           |
| Depression                                    | 21 (8.5)                              | 19 (7.7)                            |
| Anorexia                                      | 65 (26.3)                             | 62 (25.2)                           |
| Diarrhea                                      | 29 (11.7)                             | 27 (11.0)                           |
| Constipation                                  | 20 (8.1)                              | 18 (7.3)                            |
| Cough                                         | 39 (15.8)                             | 37 (15.0)                           |
| Dermatitis                                    | 67 (27.1)                             | 64 (26.0)                           |
| Injection site reaction                       | 36 (14.6)                             | 33 (13.4)                           |
| Hair loss/alopecia                            | 46 (18.6)                             | 45 (18.3)                           |
| Laboratory AEs‡                               |                                       |                                     |
| Anemia (week 1–6)†                            | 15 (6.1)                              | 16 (6.5)                            |
| Hemoglobin level: 8.5–9.9 g/dL                | 11 (4.5)                              | 13 (5.3)                            |
| Hemoglobin level: <8.5 g/dL                   | 4 (1.6)                               | 3 (1.2)                             |
| Anemia (week 6 to end-of-treatment)‡          | 50 (20.2)                             | 37 (15.0)                           |
| Hemoglobin level: 8.5–9.9 g/dL                | 33 (13.4)                             | 22 (8.9)                            |
| Hemoglobin level: <8.5 g/dL                   | 17 (6.9)                              | 15 (6.1)                            |
| Neutropenia                                   | 26 (10.5)                             | 24 (9.8)                            |
| Neutrophil count: 0.500–0.749 × 10⁹ cells/L   | 21 (8.5)                              | 20 (8.1)                            |
| Neutrophil count: <0.500 × 10⁹ cells/L        | 5 (2.0)                               | 4 (1.6)                             |
| Thrombocytopenia                              | 25 (10.1)                             | 23 (9.3)                            |
| Platelet count: 25–49 × 10⁹ cells/L           | 22 (8.9)                              | 21 (9.1)                            |
| Platelet count: <25 × 10⁹ cells/L             | 3 (1.2)                               | 2 (0.8)                             |
| ALT elevation                                 |                                       |                                     |
| >2 times ULN                                  | 35 (14.2)                             | 34 (13.8)                           |
| >5 times ULN                                  | 5 (2.0)                               | 4 (1.6)                             |
| Total bilirubin elevation||                   |                                       |                                     |
| >2 mg/dL                                      | 11 (4.5)                              | 9 (3.7)                             |
| >5 mg/dL                                      | 0 (0.0)                               | 0 (0.0)                             |

**Table 5. Adverse Events, Dose reduction and Treatment Discontinuation in Treated Patients.** Peg-IFN: peginterferon; RBV: ribavirin; AE: adverse event; ALT: alanine aminotransferase; ULN: upper limit of normal. †Values are numbers (percentages). ‡Weight-based RBV arm: major depression at week 8 of treatment, and anxiety disorder at week 7 of treatment, respectively. Flat-dose RBV arm: peripheral edema at week 14 of treatment. All of the 3 patients were considered treatment-related. §The grading of the laboratory AEs was shown for patients with the on-treatment nadir level. ¶Anemia was defined as a nadir hemoglobin level <10.0 g/dL. ||No patient with total bilirubin elevation had concomitant ALT elevation >5 times ULN.
Figure 2. Study Design. Peg-IFN: peginterferon, RBV: ribavirin; RVR: rapid virologic response, ETVR: end-of-treatment virologic response, SVR$_{24}$: sustained virologic response 24 weeks off-therapy.

chi-square with Fisher’s exact test. All statistical tests were two-tailed and the results were considered to be statistically significant when a P value was <0.05.

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Author Contributions
C.H.L., C.F.H., W.L.C., J.H.K. and M.L.Y. designed the study; C.H.L., C.F.H., W.L.C., J.H.K. and M.L.Y. analyzed and interpreted data; C.H.L., C.F.H., C.J.L., W.L.C., J.H.K. and M.L.Y. drafted the article; C.H.L., C.F.H., C.J.L., C.Y.D., J.F.H., J.W.L., C.C.L., S.S.Y., C.L.L., T.H.S., H.C.Y., P.J.C., D.S.C., W.L.C., J.H.K. and M.L.Y. revised and approved the article for important intellectual content; C.H.L., C.F.H., C.J.L., C.Y.D., J.F.H., J.W.L., C.C.L., S.S.Y., C.L.L., T.H.S., H.C.Y., P.J.C., D.S.C., W.L.C., J.H.K. and M.L.Y. provided the study materials or patients; C.H.L., C.F.H., J.W.L., J.H.K. and M.L.Y. performed statistics; C.H.L., C.F.H., J.H.K. and M.L.Y. obtained funding; J.H.K. and M.L.Y. provided administrative, technical or logistic support; C.H.L., C.F.H., J.W.L., J.H.K. and M.L.Y. collected and assembled data.

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