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Personalized Therapy of Chronic Hepatitis C and B Dually Infected Patients With Pegylated Interferon Plus Ribavirin

A Randomized Study

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Abstract: We aimed to investigate whether response-guided therapy (RGT) with peginterferon-alpha plus ribavirin by using hepatitis C virus (HCV) genotype, pretreatment HCV RNA levels, and rapid virological response (RVR, undetectable HCV RNA at treatment week 4) could be applied for active HCV/hepatitis B virus (HBV) dually infected patients, without compromised the treatment efficacy.

A total of 203 patients, seropositive of HCV antibody, HCV RNA and HBV surface antigen (HBsAg), and seronegative for HBV e antigen for >6 months, were randomized to receive peginterferon-alpha/ribavirin by either genotype-guided therapy (GGT, n = 102: HCV genotype 1 [HCV-1], 48 weeks; HCV-2/3, 24 weeks) or RGT (n = 101: HCV-1, 48 or 24 weeks if patients with baseline VL <400,000 IU/mL and RVR; HCV-2/3, 24 or 16 weeks if patients with RVR). The primary endpoint was HCV-sustained virological response (SVR).

The HCV SVR rate was comparable between the GGT (77.5%, 79/102) and RGT groups (70.3%, 71/101, $P = 0.267$), either among HCV-1/HBV (69.4% [43/62] vs 63.5% [40/63], $P = 0.571$) or among HCV-2/3/HBV (90.0% [36/40] vs 81.6% [31/38], $P = 0.342$) dually infected patients based on intention-to-treat analysis. In HCV-1/HBV dually infected patients, RVR (odds ratio [OR]: 6.05; 95% confidence intervals [CI]: 2.148–17.025, $P = 0.001$) and lower pretreatment blood glucose levels (OR: 0.97; CI: 0.944–0.989, $P = 0.003$) were independent predictors of HCV SVR. Although RVR (OR: 10.68; CI: 1.948–58.514, $P = 0.006$) was the only significant factor associated with HCV SVR in HCV-2/3/HBV dually infected patients. HBsAg loss at 1 year posttreatment was observed in 17 of 185 (9.2%) patients. The rates of discontinuation and adverse events were similar between the 2 groups.

RGT with peginterferon-alpha/RBV may be considered for HBeAg-negative HBV/HCV dually infected patients.

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Abbreviations: AE = adverse event, Anti-HCV = HCV antibodies, DAA = directly acting antiviral agent, EOTVR = end-of-treatment virological response, EVR = early virological response, GGT = genotype-guided therapy, HBeAg = hepatitis B e antigen, HBsAg = HBV surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HCV-1 = HCV genotype 1, ITT = intent-to-treat, LVL = low baseline viral load, Peg-IFN = PEGylated interferon-alpha, PP = per-protocol, RBV = ribavirin, RGT = response-guided therapy, RVR = rapid virological response, SAE = serious adverse events, SVR = sustained virological response, ULN = upper limit of normal, VL = viral load.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the leading causes of liver cirrhosis and hepatocellular carcinoma.[1,2] In HBV and HCV high endemic areas, such as the Asia-Pacific region, dual infection with HBV and HCV is not uncommon. Approximately 10% of patients are dually infected with both viruses in Taiwan.[3] Dually infected patients have been at a much higher risk for the aggravation and progression of liver disease than those with monoinfection.[4,5]

Current guidelines for the management of HBV/HCV dual infections suggest that which virus is dominant for patients with concurrent HBV/HCV dual infections should be determined and to accordingly treat patients as monoinfections.[6] PEGylated interferon (Peg-IFN) and ribavirin (RBV) combination therapy is the currently standard of care for HBV/HCV dually infected

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patients with active hepatitis C: 48 weeks of Peg-IFN/RBV for HCV genotype 1 (HCV-1)/HBV dually infected patients and 24 weeks of Peg-IFN/RBV for HCV-2/HBV dually infected patients.[7] With the strategy of genotype-guided therapy (GGT), the sustained virological response (SVR) rate of HCV was comparable between HCV/HBV dually infected patients and HCV-monoinfected patients (around 75% for HCV-1 and 85% for HCV-2, respectively).[8] Additionally, IFN plus RBV therapy also effectively suppressed HBV replication. Long-term follow-up studies in HBV/HCV dually infected patients also revealed a high cumulative hepatitis B surface antigen (HBsAg) seroclearance rate after IFN/RBV therapy.[9,10]

Response-guided therapy (RGT) based on on-treatment virological responses has achieved comparable efficacy for HCV monoinfected patients when compared to those with standard duration of Peg-IFN/RBV. A similar SVR rate between 24 and 48 weeks Peg-IFN/RBV therapy was observed in HCV-1 monoinfected patients with low baseline viral loads (LVLs) and a rapid virological response (RVR).[11–14] Similarly, 16 weeks of Peg-IFN plus weight-based RBV is recommended for HCV-2/3 patients with an RVR.[14–18] However, whether the concept of RGT with Peg-FIN/RBV can be applied in patients with HBV/HCV dual infections with active hepatitis C has not been studied.

This randomized-controlled study aimed to investigate the efficacy of a tailored regimen of Peg-IFN/RBV based on RGT in the treatment of patients with HBV and active HCV dual infections.

MATERIALS AND METHODS

Study Population

This is an open label, randomized-controlled, comparative trial, conducted in a medical center in the Southern Taiwan. Eligible subjects were previously untreated patients or had previously failed interferon monotherapy with chronic HBV/HCV dual infections, aged 18 to 65 years, who were seropositive for HBsAg, HCV antibodies (Anti-HCV) and HCV RNA for >6 months; were seronegative for hepatitis B e antigen (HBeAg); and serum alanine aminotransferase levels between 1 and 10-fold of the upper limit of normal (ULN). Other eligibility criteria included neutrophil count $>1500\,mm^3$, platelet count $>9 \times 104\,mm^3$, hemoglobin level >12 g/dL for men and >11 g/dL for women, no pregnancy or lactation, and the use of a reliable method of contraception.

The exclusion criteria included human immunodeficiency virus infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, α1-antitrypsin deficiency, overt hepatic failure, psychiatric condition, previous liver transplantation, with evidence of hepatocellular carcinoma, decompensated liver disease (Child–Pugh score ≥7); pregnant or breast-feeding women; serum creatinine ≥2 mg/dL; evidence of alcoholism or drug abuse; any other known disease that was not suitable for Peg-IFN therapy.

Study Design

The study design is illustrated in Figure 1. Eligible subjects were randomized into 2 groups at treatment initiation. Subjects who were randomized into the GGT group received Peg-IFN and weight-based dose RBV (1000–1200 mg/day) for 48 weeks in subjects dually infected with HCV-1/HBV or Peg-IFN and fixed low dose RBV (800 mg/day) for 24 weeks in subjects dually infected with HCV-2/3/HBV; the patients were then followed for 6 months. For subjects who were randomized into the RGT group, all patients were treated with Peg-IFN and weight-based RBV. For HCV-1/HBV dually infected patients, treatment duration was 24 weeks for patients with a low LVL (LVL, <400,000 IU/mL, defined based on our previous study[11])

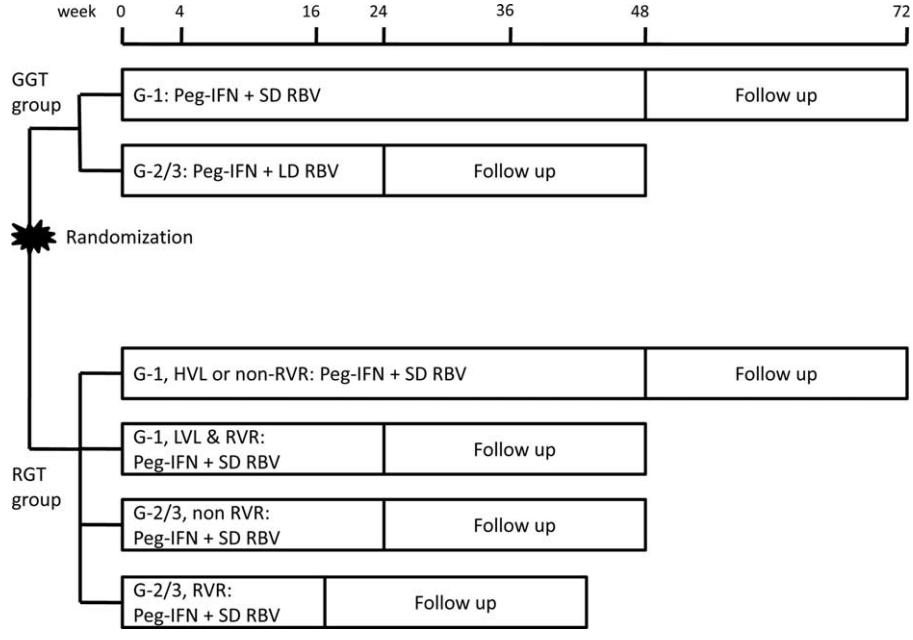

FIGURE 1. Study design of the open label, randomized-controlled, comparative trial. G-1 = genotype 1, G-2/3 = genotype 2/3, GGT = genotype guided therapy, HVL = high viral load, pretreatment HCV RNA >400,000 IU/mL, LD RBV = low dose ribavirin, 800 mg/day, LVL = low viral load, pretreatment HCV RNA ≤400,000 IU/mL, RGT = response guided therapy, RVR = rapid virological response, HCV RNA <50 IU/mL at treatment week 4, SD RBV = standard dose ribavirin, 1000-1200 mg/day.

and RVR (HCV RNA undetectable at treatment week 4); the others were treated with 48-week regimen. For HCV-2/3/HBV dually infected patients, the treatment duration was 16 weeks for patients with RVR; the others were treated with 24 weeks. The randomization was performed by computer software.

Laboratory Testing

HBsAg, HBeAg, and anti-HBe were tested using commercially available enzyme-linked immunosorbent assay kits (Abbott Laboratories, North Chicago, IL). Anti-HCV was determined by a third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL). HCV RNA was measured using a qualitative polymerase chain reaction assay (CobasAmplicor Hepatitis C Virus Test, version 2.0; Roche Diagnostics, Branchburg, NJ; detection limit: 50 IU/mL). Serum levels of HCV RNA were quantified by the branched DNA assay (Versant HCV RNA3.0, Bayer, Tarrytown, NJ; quantification limit: 615 IU/mL) if qualitative HCV RNA seropositivity. HCV genotypes were determined using the method described by Okamoto et al.[19] Serum HBV DNA levels were determined using the CobasAmpliPrep/CobasTaqMan HBV assay (CAP/CTM version 2.0, Roche Diagnostics, Indianapolis, IN; dynamic range 20 IU/mL–1.7×10^8IU/mL).

Treatment Responses

The primary endpoint was HCV SVR, defined as HCV RNA negativity 24 weeks after the end-of-treatment. On-treatment HCV virological responses included RVR (defined as HCV RNA negativity at treatment week 4), early virological response (EVR, defined as HCV RNA negativity at treatment week 12), and end-of-treatment virological response (EOTVR, defined as HCV RNA negativity at treatment cessation).

The study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the local ethics committees. Written informed consent was obtained from all patients.

Statistics

The primary efficacy was analyzed using the intent-to-treat (ITT) analysis. Patients who received at least 1 dose of the study medication would be included into the ITT analysis. Per-protocol (PP) analysis was also performed in population who had received 80-80-80 adherence and with HCV RNA available 24 weeks after EOT. Safety analysis included any patient who had received at least 1 dose of study medication. According to the publications from Taiwan[11,12,18] and an estimated 3:2 ratio of enrolled patients with genotype 1 and genotype 2/3, we assumed a difference of SVR rate of 13% between GGT and RGT groups. Using the assumption, a sample size of 95patients per group will provide a statistical power of at least 80% to detect a between group difference at the significant level of 0.05. A withdrawal rate of 5% will be allowed and the sample size will be finally set at 100 patients per group.

Continuous variables were expressed as the mean ± stan-standard deviation or the median (25th, 75th percentile). The Student's *t*-test and Mann–Whitney *U* test were used to compare continuous variables and the Chi-square and Fisher exact tests were used to compare categorical variables. Binary logistic regression analysis was used to identify the independent factors associated with SVR. All tests were 2-sided and $P < 0.05$ was considered statistically significant. All analyses were performed using the SPSS ver17.0 statistical package (SPSS, Inc., Chicago, IL).

RESULTS

Demographics and Comparison of Baseline Characteristics

A total of 203 patients were enrolled into the study, 102 in GGT group and 101 in RGT group. Of GGT group, 62 patients were HCV-1 and 40 were HCV-2/3. Of RGT group, 63 patients were HCV-1 and 38 were HCV-2/3 (Fig. 2). Table 1 showed the demographics of all the patients and the comparison of

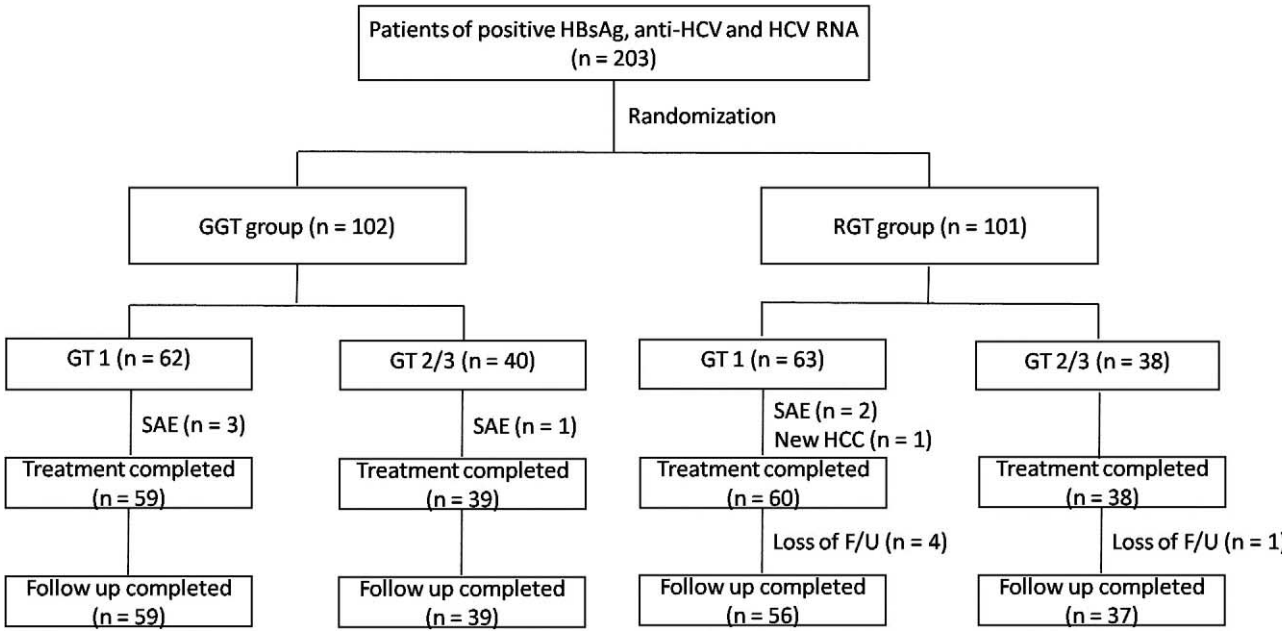

FIGURE 2. Patient flowchart. F/U = follow-up, GGT = genotype guided therapy, GT = genotype, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, RGT = response guided therapy, SAE = serious adverse event,.

TABLE 1. Demographics and Comparison of Baseline Characteristics Between Genotype-Guided and Response-Guided Group

	Genotype-Guided Group (N = 102)	Response-Guided Group (N = 101)	*P*
Male sex	59 (57.8)	71 (70.3)	0.079
Age, years	53.2 ± 11.7	51.6 ± 11.2	0.337
BW, kg	68.2 ± 10.8	66.3 ± 13.2	0.285
AST, U/L	91.2 ± 66.0	77.4 ± 50.3	0.097
ALT, U/L	130.3 ± 104.1	114.3 ± 89.6	0.243
Cr, mg/dL	0.8 ± 0.2	0.9 ± 0.2	0.114
Glucose, mg/dL	101.4 ± 23.9	105.1 ± 36.6	0.410
WBC, /μL	5804 ± 1733	5583 ± 1612	0.348
Hb, g/dL	14.4 ± 1.5	14.3 ± 1.3	0.812
PLT, 10^3/μL	160 ± 52	165 ± 59	0.543
HCV RNA, $\log_{10}$ IU/mL	5.5 ± 1.0	5.3 ± 1.0	0.155
Peg-IFN alpha-2a	52 (51.0)	43 (42.6)	0.261

Missing data – GT 1 – glucose: 3 (fixed: 1, tailored: 2). GT 2 – glucose: 5 (fixed: 4, tailored: 1). Continuous variables were expressed with mean ± SD and statistic with Student's *t*-test. Categorical variable was expressed with number (percentage) and statistic with Chi-square and Fisher exact test. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BW = body weight, Cr = creatinine, Hb = hemoglobin, HCV = hepatitis C virus, Peg-IFN = PEGylated interferon, PLT = platelet, WBC = white blood count.

baseline characteristics between GGT and RGT groups. The baseline characteristics were comparable between the 2 groups.

HCV Response

The HCV treatment response was shown in Table 2. In the ITT analysis, for patients of HCV-1/HBV, 59.7%, 83.9%, 88.7%, and 69.4% of patients in the GGT group compared with 44.4%, 92.1%, 93.7%, and 63.5% of the patients in the RGT group achieved RVR, EVR, EOTVR, and SVR ($P = 0.108$, 0.180, 0.363, and 0.571), respectively. For patients of HCV-2/3/HBV, 95.0%, 97.5%, 97.5%, and 90.0% of patients in the GGT group compared with 84.2%, 97.4%, 94.7%, and 81.6% of patients in the RGT group achieved RVR, EVR, EOTVR, and SVR ($P = 0.149$, 1.000, 0.610, and 0.342), respectively. Taken together, 77.5% of patients in the GGT group compared with 70.3% of patients in the RGT group achieved HCV SVR in the ITT analysis ($P = 0.267$), respectively.

A total of 12 patients, who did not receive 80-80-80 adherence or without HCV RNA available 24 weeks after EOT, were not included into PP analysis. In the PP analysis, for patients of HCV-1/HBV, 62.7%, 88.1%, 93.2%, and 72.9% of patients in the GGT group compared with 44.6%, 96.4%, 98.2%, and 71.4% of patients in the RGT group achieved RVR, EVR, EOTVR, and SVR ($P = 0.063$, 0.164, 0.365, and 1.000), respectively. For patients of HCV-2/3/HBV, 94.9%, 100%, 100%, and 92.3% of patients in the GGT group compared with 86.5%, 97.3%, 94.6%, and 83.8% of patients in the RGT group achieved RVR, EVR, EOTVR, and SVR ($P = 0.256$, 0.487, 0.234, and 0.303), respectively. Taken together, 80.6% of patients in the GGT group compared with76.3% of patients in the RGT group achieved HCV SVR in the PP analysis ($P = 0.487$), respectively.

Factors Associated With HCV SVR

The factors associated with SVR were further analyzed. In univariate analysis, pretreatment low serum glucose levels ($P = 0.006$), low HCV RNA levels ($P = 0.002$), and RVR ($P < 0.001$) were factors associated with HCV SVR in HCV-1/HBV dually infected patients. The multivariate analysis showed that only pretreatment low serum glucose levels (OR: 0.97, 95%CI: 0.944–0.989, $P = 0.003$) and RVR (OR: 6.05, 95%CI: 2.148 – 17.025, $P = 0.001$) were independently associated factors (Table 3). For HCV-2/3/HBV dually infected patients, the univariate analysis identified RVR ($P = 0.012$) as the only factor associated with HCV SVR. Further multivariate analysis demonstrated that RVR (OR: 10.68, 95%CI: 1.948–58.514, $P = 0.006$) was the only independent factors associated with HCV SVR (Table 3). We further analyzed factors

TABLE 2. Comparison of HCV Response Between Genotype-Guided and Response-Guided Groups

	HCV Genotype 1			HCV Genotype 2/3		
	GGT Group	RGT Group	*P*	GGT Group	RGT Group	*P*
ITT analysis	N = 62	N = 63		N = 40	N = 38	
RVR	37 (59.7)	28 (44.4)	0.108	38 (95.0)	32 (84.2)	0.149
EVR	52 (83.9)	58 (92.1)	0.180	39 (97.5)	37 (97.4)	1.000
EOTVR	55 (88.7)	59 (93.7)	0.363	39 (97.5)	36 (94.7)	0.610
SVR	43 (69.4)	40 (63.5)	0.571	36 (90.0)	31 (81.6)	0.342
PP analysis	N = 59	N = 56		N = 39	N = 37	
RVR	37 (62.7)	25 (44.6)	0.063	37 (94.9)	32 (86.5)	0.256
EVR	52 (88.1)	54 (96.4)	0.164	39 (100)	36 (97.3)	0.487
EOTVR	55 (93.2)	55 (98.2)	0.365	39 (100)	35 (94.6)	0.234
SVR	43 (72.9)	40 (71.4)	1.000	36 (92.3)	31 (83.8)	0.303

Categorical variable was expressed with number (percentage) and statistic with Chi-square and Fisher exact test. Intention–to-treat (ITT) analysis: patients who received at least 1 dose of the study medication. Per-protocol (PP) analysis: patients who had received 80-80-80 adherence and with HCV RNA available 24 weeks after EOT. EOTVR = end of treatment virological response, EVR = early virological response, RVR = rapid virological response, SVR = sustained virological response.

TABLE 3. Univariate and Multiple Logistic Regression Analyses of Factors Associated With HCV SVR in HCV-1, and HCV-2/3/HBV Dually Infected Patients

	HCV Genotype 1						HCV Genotype 2/3					
	SVR (N = 83)	Non-SVR (N = 42)	*P*	OR	95% CI	*P*	SVR (N = 67)	Non-SVR (N = 11)	*P*	OR	95% CI	*P*
Male sex	57 (68.7)	30 (71.4)	0.838				38 (56.7)	5 (45.5)	0.529			
Age, years	49.6 ± 10.9	53.4 ± 14.1	0.098	0.99	0.950–1.022	0.432	54.8 ± 10.0	55.1 ± 9.2	0.926			
BW, kg	68.8 ± 13.2	70.0 ± 11.2	0.617				64.9 ± 10.8	59.0 ± 7.5	0.085	1.07	0.993–1.157	0.073
AST, U/L	77.8 ± 64.9	81.1 ± 49.5	0.771				95.4 ± 59.0	80.3 ± 40.3	0.415			
ALT, U/L	123.3 ± 113.0	101.3 ± 66.8	0.248				136.6 ± 95.5	108.6 ± 66.2	0.352			
Cr, mg/dL	0.9 ± 0.2	0.9 ± 0.3	0.803				0.8 ± 0.2	0.8 ± 0.3	0.813			
Glucose, mg/dL	96.5 ± 15.9	115.9 ± 41.4	0.006	0.97	0.944–0.989	0.003	104.4 ± 36.3	100.9 ± 26.1	0.770			
WBC, /μL	6045 ± 1714	5470 ± 1555	0.070	1.00	1.000–1.001	0.057	5544 ± 1685	4825 ± 1277	0.181			
Hb, g/dL	14.7 ± 1.3	14.4 ± 1.5	0.380				14.0 ± 1.3	14.0 ± 1.2	0.889			
PLT, 10^3/μL	174 ± 49	160 ± 62	0.171				155 ± 58	139 ± 44	0.404			
HCV RNA, $\log_{10}$ IU/mL	5.4 ± 1.1	5.9 ± 0.7	0.002	0.81	0.451–1.446	0.471	5.2 ± 0.9	5.5 ± 0.9	0.394			
LVL	37 (44.6)	16 (38.1)	0.567									
Peg-IFN alpha-2a	41 (49.4)	16 (38.1)	0.258				33 (49.3)	5 (45.5)	1.000			
RBV, mg/kg	14.3 ± 4.8	12.9 ± 3.8	0.111				13.5 ± 4.2	14.5 ± 5.1	0.478			
RVR	54 (65.1)	11 (26.2)	<0.001	6.05	2.148–17.025	0.001	63 (94.0)	7 (63.6)	0.012	10.68	1.948–58.514	0.006
RGT group	40 (48.2)	23 (54.8)	0.571				31 (46.3)	7 (63.6)	0.342			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BW = body weight, Cr = creatinine, Hb = hemoglobin, LVL = low viral load, PLT = platelet, RBV = ribavirin, RGT = response guided therapy, RVR = rapid virological response, WBC = white blood count.

associated with HCV SVR in GGT and RGT groups, independently (Table 4). For HCV/HBV dually infected patients in GGT group, the multivariate analysis showed that RVR (OR: 18.92, 95%CI: 4.689–76.354, $P < 0.001$) was the only factor associated with HCV SVR. By contrast, for those in RGT group, multivariate analysis demonstrated that pretreatment HCV RNA level (OR: 0.49, 95%CI: 0.256–0.934, $P = 0.030$) was the only factor independently associated with HCV SVR.

HBV Response

A total of 139 patients with baseline HBV DNA available demonstrated that HBV DNA was detectable among 45 (32.4%) patients (mean, 3.9 $\log_{10}$ IU/mL, range 1.8–7.9 $\log_{10}$ IU/mL), with no difference between the 2 groups (Table 5). At the end-of-treatment, the HBV DNA was detectable among 13 (18.6%) patients in GGT group (mean, 3.3 $\log_{10}$ IU/mL, range 2.1–6.0 $\log_{10}$ IU/mL) and 15 (21.7%) patients in RGT group (mean, 3.4 $\log_{10}$ IU/mL, range 1.8–7.9 $\log_{10}$ IU/mL, $P = 0.772$). At 24 weeks posttreatment, the HBV DNA was detectable among 28 (40.0%) patients in GGT group (mean, 3.7 $\log_{10}$ IU/mL, range 2.2–7.1 $\log_{10}$ IU/mL) and 16 (23.2%) patients in RGT group (mean, 3.5 $\log_{10}$ IU/mL, range 2.1–7.9 $\log_{10}$ IU/mL, $P = 0.678$). Among 94 patients with undetectable HBV DNA at baseline, reappearance of HBV DNA was found in 7 (7.4%) of the 94 patients at the end-of-treatment and in 18 (19.1%) at 24 weeks posttreatment. Significantly higher rate of HBV DNA reappearance at 24 weeks posttreatment was observed in the GGT group than in the RGT group (32.6% vs 6.2%, $P = 0.001$). Six (33.3%) of the 18 patients with HBV DNA reappearance at 24 weeks posttreatment had reappeared HBV DNA level greater than 2000 IU/mL and all of them were in the GGT group. Among 45 patients with baseline detectable HBV DNA, 24 (53.3%) and 20 (44.4%) had HBV DNA undetectable in 24 at the end-of-treatment and in 24 weeks posttreatment, respectively. The rate of HBV DNA undetectable 24 weeks posttreatment did not differ between GGT (45.8%) and RGT (38.1%) groups. Among 45 patients with baseline detectable HBV DNA, none had increased HBV DNA level greater than 1 $\log_{10}$ IU/mL at the end-of-treatment and 2 had increased HBV DNA level greater than 1 $\log_{10}$ IU/mL 24 weeks posttreatment.

HBsAg loss was observed in 17 (9.2%) of the 185 patients who had HBsAg data available 1 year posttreatment, including 9 (9.5%) of the 95 patients in GGT group and 8 (8.9%) of the 90 patients in RGT group ($P = 1.000$).

Safety Profile

The type of adverse events (AEs) in dual-infected patients were similar to those seen in HCV-monoinfected patients. There was no difference of incidence of AEs, serious adverse events (SAE), and dose modification between GGT and RGT groups (Table 6). A total of 13 patients, 5 in GGT and 8 in RGT groups happened SAE during study period. Seven of the 13 patients with SAE, 4 in GGT and 3 in RGT groups, discontinued Peg-IFN/RBV therapy.

Notably, there were 3 patients experienced severe acute hepatitis flare (alanine aminotransferase level >10-folds ULN and total bilirubin level >2-folds ULN) correlated to HBV DNA surge within 48 weeks posttreatment. One patient suffered from liver decompensation related to HBV cirrhosis. All of the 4 patients received NUC therapy immediately and were well controlled thereafter. Another patient had severe liver decompensation which was not related to HBV (HBV DNA level less than 60 IU/mL) at 4th week of Peg-IFN/RBV therapy and died within 1 month.

DISCUSSION

The current study demonstrated that the concept of RGT for HCV-monoinfected patients might also be applied in HBeAg-negative HBV/HCV dually infected patients with an HCV SVR rate of 63.5% in HCV-1/HBV and 81.6% in HCV-2/3/HBV dually infected patients.

In HCV monoinfected patients, a fixed duration therapy with Peg-IFN/RBV achieved approximately 50% SVR in HCV-1 and 83% SVR in HCV-2/3 patients in Western countries.[16,17,20–24] For Asian patients with HCV monoinfection, better SVR rates of approximately 77% in HCV-1 and over 90% in HCV-2/3 patients have been observed.[18,25] Different patterns of on-treatment virological responses have been reported.[26] A shortened duration of 24-week Peg-IFN/RBV therapy could achieve a comparable SVR rate with standard 48-week therapy for HCV-1 patients with pretreatment LVL and RVR.[11–14] Similarly, 16 weeks of Peg-IFN combined with standard dose of RBV had a noninferior SVR rate compared with 24-week therapy for HCV-2/3 patients with RVR in meta-analysis.[14] Therefore, Peg-IFN/RBV RGT for HCV monoinfection was recommended in European and Asian-Pacific guidelines in the era before directly acting antiviral agents (DAAs) were available.[6,27]

For HBV/HCV dually infected patients with active hepatitis C, the treatment duration and efficacy of Peg-IFN/RBV therapy has recently confirmed.[8,27,28] A Taiwanese multicenter clinical trial demonstrated that 48 and 24 weeks of Peg-IFN/RBV therapy achieved similar HCV SVR rate between HCV/HBV dually infected and HCV-monoinfected patients, for HCV-1 or HCV-2/3 infections, respectively.[8] The following study also revealed a durable HCV SVR in 97% of patients during long-term follow-up.[10] Similar results were also reported from Europe and Korea.[29,30] However, these results were based on an HCV GGT with fixed duration of Peg-IFN/RBV, 48 weeks in HCV-1 and 24 weeks in HCV-2/3 patients. Whether a tailored abbreviated treatment regimen using the concept of RGT for patients with RVR could be applied for HBV/HCV dually infected patients has never been studied.

The current study first demonstrated that a tailored duration of Peg-IFN/RBV therapy according to pretreatment viral load (VL) and RVR had comparable HCV SVR rates compared with fixed duration of GGT in HBV/HCV dually infected patients with either HCV-1 or HCV-2/3 infections. These findings indicated that the strategies of RGT for HCV monoinfection could also be translated to HBV/HCV dual infections.

We also observed that pretreatment low glucose levels and RVR were factors associated with SVR in dually infected patients with HCV-1/HBV dually infections, and RVR was the only factor associated with SVR in patients with HCV-2/3 infections. These findings echoed the impact of insulin resistance on the treatment response to Peg-IFN/RBV for HCV-1-monoinfected patients[31] and the leading role of RVR in determining the SVR to Peg-IFN/RBV therapy for HCV-monoinfected patients.[32]

Interactions between HBV and HCV are important issues in dually infected patients. HBsAg loss and DNA suppression following Peg-IFN/RBV have been observed. By contrast, reappearance of HBV DNA might occur in patients with pretreatment undetectable HBV DNA.[8] In the current study, the rate of HBsAg loss was similar between GGT and RGT groups, both were comparable with previous reports.[10,33] The rate (19.1%) of posttreatment HBV reappearance in patients with baseline

TABLE 4. Univariate and Multiple Logistic Regression Analyses of Factors Associated With HCV SVR of HCV/HBV Dually Infected Patients in GGT and RGT Groups

	Genotype-Guided Therapy						Response-Guided Therapy					
	SVR (N = 79)	Non-SVR (N = 23)	*P*	OR	95% CI	*P*	SVR (N = 71)	Non-SVR (N = 30)	*P*	OR	95% CI	*P*
Male sex	46 (58.2)	13 (56.5)	1.000				49 (69.0)	22 (73.3)	0.813			
Age, years	52.5 ± 11.1	55.4 ± 13.5	0.301				51.3 ± 10.4	52.5 ± 13.0	0.611			
BW, kg	68.3 ± 11.3	67.6 ± 9.2	0.781				65.7 ± 13.3	67.8 ± 12.9	0.463			
AST, U/L	88.9 ± 69.8	99.1 ± 51.5	0.519				81.9 ± 54.0	67.0 ± 39.4	0.178			
ALT, U/L	129.3 ± 111.1	133.6 ± 76.9	0.865				129.2 ± 99.4	79.3 ± 44.9	0.001	1.01	1.000–1.020	0.060
Cr, mg/dL	0.8 ± 0.2	0.9 ± 0.2	0.714				0.9 ± 0.2	0.9 ± 0.3	0.884			
Glucose, mg/dL	99.8 ± 23.4	106.9 ± 25.4	0.222				100.0 ± 30.5	117.6 ± 47.1	0.075			
WBC, /μL	6028 ± 1800	5034 ± 1228	0.004				5591 ± 1593	5567 ± 1684	0.946			
Hb, g/dL	14.4 ± 1.5	14.3 ± 1.3	0.723				14.3 ± 1.2	14.4 ± 1.6	0.719			
PLT, 10^3/μL	165 ± 52	145 ± 50	0.108				166 ± 56	164 ± 65	0.876			
HCV genotype 1	43 (54.4)	19 (82.6)	0.016	0.68	0.158–2.882	0.596	40 (56.3)	23 (76.7)	0.072			
HCV RNA, $\log_{10}$ IU/mL	5.5 ± 1.0	5.8 ± 0.7	0.163				5.1 ± 1.0	5.8 ± 0.8	0.001	0.49	0.256–0.934	0.030
LVL	33 (41.8)	10 (43.5)	1.000				45 (63.4)	13 (43.3)	0.079			
Peg-IFN alpha-2a	39 (49.4)	13 (56.5)	0.638				35 (49.3)	8 (26.7)	0.048	2.21	0.794–6.163	0.129
RBV, mg/kg	13.2 ± 4.0	12.1 ± 4.1	0.248				14.8 ± 5.0	14.2 ± 3.9	0.554			
RVR	68 (86.1)	7 (30.4)	<0.001	18.92	4.689–76.354	<0.001	49 (69.0)	11 (36.7)	0.004	1.48	0.488–4.516	0.487

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BW = body weight, Cr = creatinine, Hb = hemoglobin, LVL = low viral load, PLT = platelet, RBV = ribavirin, RGT = response guided therapy, RVR = rapid virological response, WBC = white blood count.

TABLE 5. HBV Virological Response After PEGylated Interferon and Ribavirin Therapy

	All	GGT Group	RGT Group	*P*
Pretreatment HBV DNA, n	139	70	69	
Undetectable, n, %	94 (67.6%)	46 (65.7%)	48 (69.6%)	0.718
Detectable, n, %	45 (32.4%)	24 (34.3%)	21 (30.4%)	
mean (range), $\log_{10}$ IU/mL	3.9 (1.8–7.9)	3.9 (2.0–7.4)	3.9 (1.8–7.9)	0.955
End-of-treatment HBV DNA, n	139	70	69	
Undetectable, n, %	111 (79.9%)	57 (81.4%)	54 (78.3%)	0.677
Detectable, n, %	28 (20.1%)	13 (18.6%)	15 (21.7%)	
mean (range), $\log_{10}$ IU/mL	3.4 (1.8 – 7.9)	3.3(2.1 –6.0)	3.4(1.8 –7.9)	0.772
24 weeks posttreatment HBV DNA, n	139	70	69	
Undetectable, n, %	95 (68.3%)	42 (60.0%)	53 (76.8%)	0.045
Detectable, n, %	44 (31.7%)	28 (40.0%)	16 (23.2%)	
mean (range), $\log_{10}$ IU/mL	3.6 (2.1–7.9)	3.7 (2.2–7.1)	3.5 (2.1–7.9)	0.678
Patients with undetectable HBV DNA at baseline, n	94	46	48	
Detectable HBV DNA at the end-of-treatment, n, %	7 (7.4)	5 (10.9)	2 (4.2)	0.263
Detectable HBV DNA at 24 weeks posttreatment, n, %	18 (19.1)	15 (32.6)	3 (6.2)	0.001
Patients with detectable HBV DNA at baseline, n	45	24	21	
Undetectable HBV DNA at the end-of-treatment, n, %	24 (53.3)	16 (66.7)	8 (38.1)	0.076
Undetectable HBV DNA at 24 weeks posttreatment, n, %	20 (44.4)	11 (45.8)	8 (38.1)	0.764

GGT = genotype guided therapy, HBV = hepatitis B virus, RGT = response guided therapy.

undetectable HBV DNA and the rate (44.4%) of HBV virologic response in patients with baseline detectable HBV DNA were also consistent with previous studies. Interestingly, we found that among patients with baseline undetectable HBV DNA, GGT group had a significantly higher rate of posttreatment HBV DNA reappearance than the RGT group did. The findings implicated that close observation of certain HBV/HCV dually infected patients after Peg-IFN/RBV therapy is warranted. Fortunately, only 4 patients experienced significant HBV-related clinical reactivation. All the patients were controlled after immediately treated with HBV nucleot(s)ide analogs.

Consistent with previous studies, Peg-IFN/RBV combination therapy was well tolerated with high adherence and low discontinuation rate in the current study. The incidence and severity of AEs and laboratory abnormalities were similar to those reported previously in HCV-monoinfected patients.[34] There was also no significant difference of AEs and laboratory abnormalities between patients of GGT and RGT groups.

The substantial lower SVR rate was observed in HCV-2/3/HBV dually infected patients treated with RGT in the current study. As for HCV-2/3-monoinfected patients, an abbreviated treatment duration of Peg-IFN/RBV is not recommended for those with unfavorable predictors, such as obesity, cirrhosis, and high baseline VL, even they achieving an RVR. Nevertheless, our findings indicated that 24 and 16 weeks of Peg-IFN/RBV may be considered for low VL HCV-1/HBV and HCV-2/HBV dually infected patients, respectively, if they achieve an HCV RVR.

Recently, introduction of newly developed DAAs with or without IFN and/or RBV have a great achievement in treatment efficacy and safety for anti-HCV therapy with SVR rates of higher than 90% for HCV-1 or 2 patients.[35–37] However, there is no DAAs data available for HCV/HBV dually infected patients. Whether the high efficacy and good safety of newly introduced DAA-based therapy for HCV monoinfection could be translated to HCV/HBV dually infected patients still needs further studies. Moreover, lack of Peg-IFN effect on HBV, the safety of DAA IFN-free regimens for HCV/HBV dually infected patients, remains to be explored carefully, in terms of HBV reactivation after HCV eradication. Peg-IFN/RBV would be the mainstay for the treatment of HBV/HCV dually infected patients before new therapeutic agents with better efficacy and safety available.[38] Our data support a cost-effective strategy with Peg-IFN/RBV for the treatment of HBeAg-negative HCV/HBV dually infected patients and the chance to treat both infections at once, which may not be achieved by the new DAAs. Furthermore, in the era of new DAAs, our findings may also provide evidence to obviate unnecessary protease inhibitor[39] or to conduct RGT based on HCV genotype and pretreatment/on-treatment viral kinetics when applying DAA plus Peg-IFN/RBV combination therapy for HBeAg-negative chronic dual HCV/HBV infections.[40]

In conclusion, RGT with Peg-IFN plus RBV according to HCV genotype, baseline HCV VL and RVR had comparable efficacy as GGT for HBeAg-negative HBV/HCV dually infected patients. Strategy of RGT with abbreviated regimens may be considered for the clinical settings.

TABLE 6. Rates of Serious Adverse Events, Grade 3 or 4 Adverse Events, Dose Modification, and Adverse Events

	GGT Group N = 102	RGT Group N = 101	*P* Value
Serious adverse events, n, %	5 (4.9)	8 (7.9)	0.407
Grade 3 or 4 adverse events, n, %	43 (42.2)	36 (35.6)	0.389
Dose modification, n, %	64 (62.7)	66 (65.3)	0.770
Dose reduction, n, %	60 (58.8)	64 (63.4)	0.565
Adverse events, n, %	9 (8.8)	13 (12.9)	0.376
Laboratory abnormality, n, %	56 (54.9)	57 (56.4)	0.888
Discontinuation, n, %	4 (3.9)	3 (3.0)	1.000
Influenza-like symptoms			
Fever	4 (3.9)	6 (5.9)	0.537
Chills	8 (7.8)	7 (6.9)	1.000
Headache	25 (24.5)	18 (17.8)	0.303
Myalgia	47 (46.1)	36 (35.6)	0.154
Gastrointestinal symptoms			
Anorexia	49 (48.0)	45 (44.6)	0.674
Nausea	9 (8.8)	10 (9.9)	0.814
Diarrhea	12 (11.8)	14 (13.9)	0.680
Psychiatric symptoms			
Anxiety	25 (24.5)	24 (23.8)	1.000
Depression	26 (25.5)	20 (19.8)	0.402
Insomnia	54 (52.9)	56 (55.4)	0.779
Dermatologic symptoms			
Hair loss	48 (47.1)	43 (42.6)	0.573
Skin rash	29 (28.4)	28 (27.7)	1.000
Injection site reaction	11 (10.8)	9 (8.9)	0.814
Hematological abnormality			
Leucopenia (white cell count $<1500/mm^3$)	10 (9.8)	14 (13.9)	0.393
Anemia (hemoglobin level <10 g/dL)	44 (43.1)	52 (51.5)	0.262
Thrombocytopenia ($<50{,}000/mm^3$)	15 (14.7)	12 (11.9)	0.680

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