Randomized Controlled Trial of Pegylated Interferon-Alfa 2a and Ribavirin in Treatment-Naive Chronic Hepatitis C Genotype 6

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Hepatitis C virus (HCV) genotype is an important criteria in determining duration of therapy and predictor of sustained virologic response (SVR) to pegylated interferon (PEG IFN) and ribavirin (RBV) therapy. Optimal duration of therapy for patients with HCV genotype 6 is not known. We conducted a multicenter, open-label randomized controlled trial of patients with HCV genotype 6 at five gastroenterology clinics in the western U.S. Patients were stratified by viral load and histologic stage and assigned to receive PEG IFN-α2a 180 μg subcutaneously weekly and weight-based oral RBV 800 to 1,200 mg daily for 24 or 48 weeks. Primary outcome measurement was SVR rate by intention-to-treat analysis. From February 2005 to October 2007 a total of 60 patients (age 51 ± 10 years, 47% male, log HCVRNA 6.3 ± 1.1 IU/mL) were enrolled: 27 patients to 24 weeks and 33 patients to 48 weeks of therapy. In the 24-week and 48-week groups, 96% and 97% achieved early virologic response ($P = 0.90$); 89% versus 94% achieved end of therapy virologic response ($P = 0.48$). SVR was achieved in 70% versus 79% of patients assigned to 24 weeks versus 48 weeks ($P = 0.45$). Rapid virologic response (RVR) was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82% and 83% of those with RVR achieved SVR versus 33% and 29% for the 24-week and 48-week groups, respectively ($P = 0.07$ and $P = 0.02$). *Conclusion:* There was no significant difference in SVR rates in patients with HCV genotype 6 treated with PEG IFN-α2a and RBV for 24 versus 48 weeks. (HEPATOLOGY 2010;52:1573-1580)

Infection with hepatitis C virus (HCV) is a major cause of morbidity and mortality and affects 175 million persons worldwide.[1] Chronic hepatitis C (CHC) is common in individuals from Southeast Asia, where the prevalence of HCV ranges from 5.6% in Thailand to 6.1% in Vietnam. The overall prevalence of HCV in Asia is 3%, higher than that seen in the overall U.S. population (1.8%).[1,2]

The current standard-of-care to treat HCV-infected patients is the combination of pegylated interferon (PEG IFN) and ribavirin (RBV). Among the various viral and host factors, HCV genotype is one of the most important predictors of response to treatment and is used to guide duration of treatment. Patients with HCV genotype 1 are typically treated for 48 weeks, whereas patients with genotype 2 and 3 are treated for 24 weeks,[3,4] whereas the optimal duration of therapy for patients with HCV genotype 6 is not known.

HCV genotypes are geographically distributed throughout the world. In the U.S. and Europe, HCV genotypes 1, 2, and 3 constitute the vast majority of the infections. Data from Hong Kong, China, Vietnam, Myanmar, and immigrant populations from

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; CHC, chronic hepatitis C; ETR, end of treatment response; EVR, early virologic response; HCV, hpatitis C virus; PEG IFN, pegylated interferon; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response.

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those areas in the U.S. suggest that approximately one-third of HCV-infected patients in these areas have genotype 6 or its subtypes.[5-11] Previously known HCV genotypes 7, 8, and 9 are now recognized as subtypes of genotype 6.[12] Because of the limited geographic distribution of HCV genotype 6, there are limited data on its response to available treatment.[13-17]

In our prior retrospective study we found that patients treated with 48 weeks had higher SVR rates. However, the number of patients treated for 48 weeks was small and there was potential for bias because it was not intention-to-treat analysis.[16] Other studies of genotype 6 have used 48-52 weeks of varying IFN-based regimens and were also mostly retrospective in study design and none specially studied treatment duration as a predictor for outcomes.[3,13,15] In this prospective multicenter randomized trial, we compared whether the sustained virologic response (SVR) to combination therapy with PEG IFN-α2a and RBV for 24 weeks is equivalent to 48 weeks of therapy in patients infected with HCV genotype 6.

Patients and Methods

Eligibility Criteria. From February 2005 to October 2007, treatment-naive patients with CHC between 18 and 70 years of age at five community-based gastroenterology and liver centers in California and Texas with large concentrations of Southeast Asians were eligible for study. To be included in the study, patients must have met the following criteria: positive anti-HCV (Roche Amplicor HCV test, v. 2.0, Roche Molecular Diagnostics Systems, Branchburg, NY) and positive HCV RNA polymerase chain reaction (PCR) (Roche Monitor HCV test, Roche Molecular Diagnostics Systems) and presence of HCV genotype 6 or its subtypes (HCV Genotype Test, Quest Diagnostics, San Juan Capistrano, CA, or INNO-LiPA v. 2.0, Innogenetics, Ghent, Belgium). Patients must also have Stage 1 or more fibrosis by the Metavir scoring system[18] and evidence of chronic hepatitis on liver histology, compensated liver disease, absence of hepatocellular carcinoma by imaging studies, and alfa-fetoprotein (AFP). Patients were excluded if they were pregnant, suspected to have hypersensitivity to IFN or PEG IFN, or RBV, receiving treatment with any other systemic antiviral, antineoplastic, or immunomodulating treatment less than 6 months prior to first dose of study drug, affected with any types of liver diseases other than CHC, anemia, or having decompensated cirrhosis (Child-Pugh score >6, coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, bleeding from esophageal varices). Other exclusion criteria were coinfection with hepatitis B virus or human immunodeficiency virus, organ transplant history, and preexisting medical conditions that could interfere with subjects' participation in protocol including severe psychiatric illness or poorly controlled cardiac, pulmonary, or diabetic disease.

Intervention. This multicenter, open-label study utilized a randomized 1:1 ratio at study entry into two treatment groups using permuted block method stratified by histology staging 1-2 versus 3-4 and low versus high viral load (<800,000 IU/mL versus ≥800,000 IU/mL). Stratification by histologic staging and viral load was done as these are the strongest predictors of treatment response besides genotype.[3,4] Randomization was carried out by the lead coordinator at the central site and assignment was concealed in opaque envelopes. After written consent was obtained, eligible patients were assigned to receive PEG IFN-α2a 180 μg subcutaneously weekly and weight-based oral RBV 800 to 1,200 mg per day for 24 weeks or 48 weeks (Roche Laboratories, Nutley, NJ). Patients were followed with laboratory testing and clinical visits to assess efficacy and safety at entry, treatment weeks 2, 4, 8, at then at 4-week intervals thereafter during treatment and at week 4, 8, and 24 following end of treatment. Serum HCV RNA levels were measured at baseline, week 12, week 24, end of treatment, and 24 weeks after end of treatment. Early virologic response (EVR) was defined as having at least a 2-log reduction in serum HCV RNA levels from baseline at week 12 of therapy. After submission of initial protocol, new data suggested the predictive value of measuring rapid virologic response (RVR) defined as undetectable (<50 IU/mL) serum HCV RNA level at week 4.[19] This test was done at the discretion of the treating physicians. All subjects gave written consent. This study protocol was approved by Western Institutional Review Board (Olympia, WA).

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Assessment of Efficacy. The primary study outcome was SVR (defined as absence of HCV RNA 6 months after cessation of therapy) and by intention-to-treat analysis. Secondary outcome measurements included RVR, complete EVR (defined as absence [<50 IU/mL] of HCV RNA at week 12 of therapy), end of treatment response or ETR (defined as absence [<50 IU/mL] of HCV RNA at end of therapy), biochemical response (defined as normal serum ALT level [<40 U/L] at the end of the follow-up period), and treatment adherence (defined as completion of at least 75% of intended dosage for at least 75% of intended duration).[20] A 75% rather than 80% cutoff was used because a single dose reduction, for example, from PEG IFN 180 μg to 135 μg, represented a 25% decrease than the intended dosage. Patients with positive HCV RNA by PCR at treatment week 24 were considered nonresponders and therapy was discontinued.

Assessment of Safety. Participants were evaluated with a standardized questionnaire for adverse events (AEs) and laboratory tests on an outpatient basis to assess safety. The World Health Organization grading system was used to grade severity of AEs from mild (Grade 1) to life threatening (Grade 4). Dose reductions for PEG IFN-α2a and RBV was done for severe AEs (Grade 3) except for flu-like symptoms such as fever, chills, nausea, myalgia, arthralgia, headache unless symptoms were incapacitating despite supportive treatment. Severe AEs were defined as incapacitating events with an inability to do usual activities, events that significantly affected clinical status, and/or warranted intervention. Therapy was discontinued for life-threatening AEs (Grade 4). Patients with decreased hemoglobins (Hb) less than 11 g/dL received reduced RBV dose and thropoeitin (EPO) supplement (20,000 to 40,000 IU subcutaneously weekly), which was increased up to 60,000 IU if repeat Hb <11 and discontinued once Hb was greater than 13 g/dL. The choice of a weight-based algorithm was made by the treating physician. If Hb decreased to <8.5 g/dL, patients were discontinued from the study. RBV could be interrupted up to a maximum of 2 weeks and restarted at reduced dose after AEs resolve. For neutropenia, if absolute neutrophil count (ANC) decreased to <750 cells/μL, PEG IFN-α2a dosage was decreased from 180 μg to 135 μg and then to 90 μg weekly for second reduction if no improvement in ANC was observed. If ANC decreased below 500, PEG IFN was held for 2 weeks and resumed at 90 μg if ANC increased to greater than 1,000. Patients would be discontinued from the study if ANC remained below 500.

Statistical Analysis. We assumed an SVR of approximately 40% for the 24-week and 80% for the 48-week treatment group based on results of our previous retrospective study and other studies with HCV genotype 6.[16] With such expected SVR rates and a 2-sided alpha of 0.05, the power is 80% for a total sample size of 60 patients and approximately 30 patients in each arm. Continuous variables were compared using Student's t test if tests normality is observed, whereas nonparametric methods such as the rank sum test was used for all others. Chi-square statistics were used to compare categorical variables. Univariate and multivariate logistic regression was used to estimate adjusted odd ratios relating potential treatment predictors to SVR. Primary analysis of SVR was done by intention-to-treat. Statistical significance was defined as a two-sided P value of 0.05 or less. All statistical analysis was performed using Stata v. 9.0 (Stata Corp., College Station, TX).

Results

Patient Characteristics. The study flow diagram is shown in Fig. 1. Of the 75 patients screened, 60 patients were included in the trial from five clinical sites. Twenty-seven patients were randomly assigned to 24 weeks of treatment and 33 patients were assigned to 48 weeks of treatment. All except one patient were of Asian descent and 93% of patients were Vietnamese or Chinese Vietnamese immigrants. The one non-Asian patient was a Hispanic woman in the 24-week group. As shown in Table 1, baseline characteristics were similar in both groups. As included in the randomization process, the proportion of patients with advanced fibrosis stage 3-4 and HCV RNA levels ≥800,000 IU/mL were similar in the 24- and 48-week groups: 26% and 27% for advanced fibrosis and 74% and 64% for high HCV RNA levels, respectively. Steatosis was noted in 33% versus 52% ($P = 0.36$) and excess iron was found in 28% versus 24% ($P = 0.35$) in the 24-week and 48-week groups, respectively. Average baseline viral loads in both groups was over 6.2 ± 1.0 log IU/mL. Seventy-eight percent of patients in the 24-week group and 82% of patients in the 48-week group adhered to the assigned duration of therapy ($P = 0.70$).

Virologic Response. RVR, complete EVR, and SVR results are shown in Fig. 2. Of the subgroup of 39 patients who had HCV RNA PCR testing at week 4 of therapy, 17 of 20 (85%) in the 24-week treatment group and 12 of 19 (63%) achieved RVR but this difference (22%, 95% confidence interval [CI]: −05% to

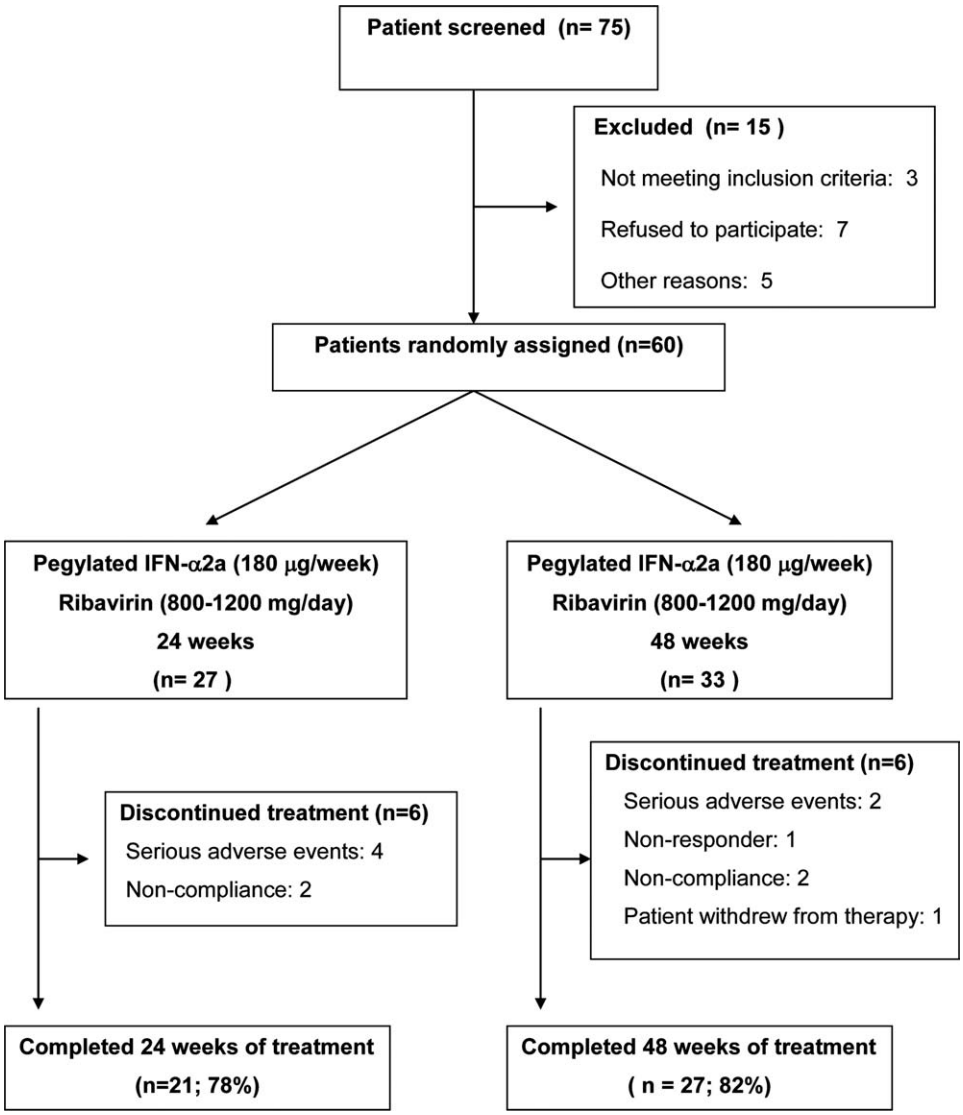

Fig. 1. Flow diagram of the clinical trial.

49%) was not statistically significant ($P = 0.12$). RVR was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 14 of 17 (82%) and 10 of 12 (83%) of those with RVR achieved SVR compared to 1 of 3 (33%) and 2 of 7 (29%) for the 24-week and 48-week groups, respectively ($P = 0.07$ and $P = 0.02$). A similar percentage of patients in both the 24-week and 48-week groups achieved complete EVR (96% versus 97%, $P = 0.90$) and ETR (89% versus 94%, $P = 0.48$). Only one patient in the 24-week and 48-week groups did not achieve complete EVR but the patient in the 24-week group subsequently achieved SVR. SVR was slightly lower in the 24-week group as compared to the 48-week group (70% versus 79%) but this difference (9%, 95% CI: −31% to 14%) was not statistically significant ($P = 0.45$). Normalization of serum ALT levels 6 months after therapy was lower in the 24-week group compared to the 48-week group (78% versus 91%) but this difference (13%, 95% CI: −32% to 5%) was also not statistically significant ($P = 0.16$).

Safety and Treatment Adherence. Frequency of constitutional symptoms and laboratory abnormalities are shown in Table 2. The most common side effects were generalized flu-like symptoms, cutaneous, and psychiatric symptoms. Anemia was more frequent in the 48-week group compared to the 24-week group (72% versus 44%, $P = 0.03$). Patients in the 48-week treatment group were also more likely to receive erythropoetin for anemia (52% versus 22%, $P = 0.02$). Neutropenia with ANC <750 occurred in 19% and 23% of patients treated for 24 weeks and 48 weeks, respectively. As shown in Table 3, treatment adherence by the 75-75-75 criteria was 63% in the 24-week group compared to 79% for the 48-week group

Table 1. Patient Demographics by Assigned Treatment Groups

Characteristics	24 Week (n = 27)	48 Week (n = 33)	*P* Value
Age (years)	49.6 ± 12.4	52.8 ± 8.0	0.23
Male sex	48%	46%	0.84
Body weight (lbs)	136 ± 23	133 ± 27	0.60
Body mass index	24.6 ± 3.8	23.6 ± 4.5	0.37
Smoking	18%	9%	0.38
Mild alcohol use	4%	9%	0.55
Pretreatment ALT (U/L)	84 ± 66	64 ± 35	0.14
Pretreatment HCV RNA (log IU/mL)	6.24 ± 1.09	6.28 ± 1.02	0.14
Low (<800,000 IU/mL)	26%	36%	0.39
High (≥800,000 IU/mL)	74%	64%	
Liver histology			
Stage	2.14 ± 1.06	2.09 ± 0.77	0.81
1-2	74%	73%	0.91
3-4	26%	27%	
Grade	2.15 ± 0.82	2.21 ± 0.82	0.77
1-2	67%	61%	0.63
3-4	33%	39%	

Values described as means ± SD or proportions (%).

($P = 0.18$). Therapy was permanently discontinued in six patients (22%) in the 24-week group and six patients (18%) in the 48-week group. In the 24-week group, four patients were discontinued for serious AEs including two patients with severe anemia, one with hyperthyroidism, one with neutropenia, and two patients for noncompliance with the protocol. In the 48-week group, two patients were discontinued for serious AEs including one with hyperthyroidism and one with severe anemia. In the same group, one patient was discontinued from therapy for being a nonresponder, two for noncompliance with the protocol, and one due to patient's desire to stop therapy.

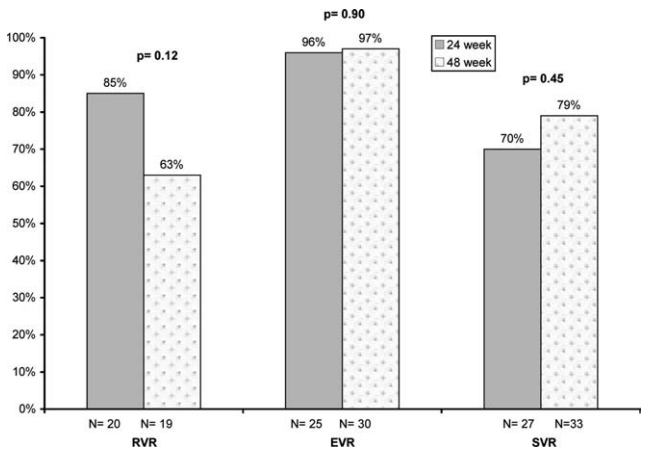

Fig. 2. Virologic response by timepoint and treatment group (RVR: rapid virologic response; EVR: complete early virologic response; SVR: sustained virologic response).

Table 2. Adverse Events by Treatment Group

Adverse Events	24-Week N = 27(%)	48-Week N = 33(%)	*P* Value
Generalized			
Myalgia	81	70	0.29
Anorexia	71	67	0.72
Headache	67	55	0.34
Nausea	67	42	0.06
Fever	59	52	0.55
Vomiting	37	18	0.10
Cutaneous			
Rash	70	76	0.64
Alopecia	56	61	0.69
Injection site irritation	44	51	0.59
Psychiatric			
Insomnia	59	48	0.41
Depressed mood	40	24	0.17
Others			
Shortness of breath	48	61	0.34
Chest pain	33	33	0.99
Hematologic			
Anemia (Hb < 11 g/dL)	44	72	0.03
Neutropenia (ANC < 750 cells/μL)	19	23	0.66
Thrombocytopenia (platelet < 50 cells/μL)	4	0	0.26
Serious adverse event % (n)	15 (4)	6 (2)	
Severe anemia (Hb < 8.5 g/dL)	2	1	
Hyperthyroidism	1	1	
Neutropenia (ANC < 500 cells/ μL)	1	0	

*Hb, hemoglobin; ANC, absolute neutrophil count.

Predictors of SVR. Potential predictors of SVR including male sex, increasing age, EVR, and assigned treatment duration (48 weeks versus 24 weeks) were examined. None of the predictors were significant on univariate or multivariate analysis. The odds ratio (OR) relating treatment duration (48-week versus 24-week) to SVR was 1.19 (95% CI = 0.32-4.48). EVR was not a statistically significant predictor for SVR (OR = 3.85 (0.22-67.75) $P = 0.36$). In a separate multivariate analysis of potential predictors of SVR of all of the 39 patients tested for RVR, OR relating RVR to SVR was 19.7 (2.5-152.7) after controlling for male sex (OR = 1.36 (0.23-7.95), increasing age (OR = 0.92 (0.84-1.02), and treatment duration (OR = 1.56 (0.26-9.55).

Table 3. Treatment Adherence by Treatment Group

	24-Week *N* = 27(%)	48-Week *N* = 33(%)	*P* Value
Treatment adherence (75/75/75)*	63	79	0.18
PEG-IFN α-2a dose reduction	19	18	0.97
Ribavirin dose reduction	41	39	0.92
Erythropoetin use	22	52	0.02
Discontinuation of therapy	22	18	0.70

*Treatment adherence defined as completion of at least 75% of intended dosage for at least 75% of intended duration.

Discussion

To our knowledge, this is the largest and only prospective randomized controlled trial of treatment efficacy of PEG IFN-α2a and RBV in patients with HCV genotype 6. This is also the only study to directly evaluate 24 weeks of combination therapy versus 48 weeks of combination therapy by intention-to-treat analysis. In this study, 24 weeks of therapy with PEG IFN with RBV resulted in an SVR of 70% compared to 79% in patients who received 48 weeks of therapy. Although the SVR rate was slightly greater in the 48-week group, 48 weeks of therapy was not statistically superior to 24 weeks of combination therapy. Regardless of whether patients were assigned to 24 or 48 weeks of combination therapy, the 70%-79% response rate in our study appears to be significantly higher than the 40%-50% response rate observed in CHC genotype 1 patients and more similar to the 70%-80% response rate of CHC genotypes 2 and 3 seen in registration trials of CHC.[3,4,21] Our reported SVR rate is also similar to randomized controlled trials of genotype 1 in Asian populations, which have reported SVR rates of 60% to 79%.[22-24]

The SVR reported in the 24-week group in our current study is significantly greater than our prior retrospective study in which we reported an SVR of 39% compared to 75% in patients who received 48 weeks of therapy.[16] However, in our prior study there were only 23 patients in the 24-week group and only 12 patients in the 48-week group. In addition, patients treated for the 24-week duration were treated shortly after the approval of combination therapy with less awareness of optimal management of side effects. In addition, our prior study was not randomized or analyzed as intention-to-treat, so there was likely some bias to explain the discrepancy. The SVR rates reported in our current study is likely more representative of true SVR of patients with HCV genotype 6 treated for 24 weeks of combination therapy. The generalized, cutaneous, and psychiatric side effects reported in study have been previously reported in other studies of PEG IFN and RBV for the treatment of CHC.[3,4,21,25] Anemia (Hb <11 g/dL) was more common in patients treated for 48 weeks with combination therapy, and patients in this group were more likely to require erythropoetin. This is not unexpected, as anemia is a common side effect and may be more common in patients treated for 48 weeks due to longer exposure to RBV.

Prior studies of HCV genotype 6 and its subtypes only include patients treated for 48 to 52 weeks. In a study from Hong Kong, Hui et al.[15] reported an SVR of 62.5% in 16 patients with genotype 6 compared to 29.2% in 24 patients with genotype 1 treated with 3 million units of standard IFN and weight-based RBV for a total of 52 weeks. In a retrospective study in Australia, Dev et al.[13] reported an SVR of 83% in 40 patients with genotypes 6, 7, 8, or 9 compared to 62% for patients with HCV genotype 1. In this study, patients were first treated with an induction dose of IFN 5 million units daily for 8 weeks followed by the standard dose of 3 million units three times a week and ribavirin 1,000-1,200 mg a day for 44 weeks. The reported SVR for CHC genotype 1 in this study is higher than those reported in registration trials for both IFN+RBV and PEG IFN+RBV combinations. It is not clear whether induction or higher doses of IFN and/or RBV may explain this finding. Although older studies only included standard IFN+RBV, Fung et al.[14] evaluated the efficacy of PEG IFN and oral RBV in patients with genotype 6. In this study, the reported SVR was 86% in 21 patients with HCV genotype 6 compared to 52% in 21 patients with HCV genotype 1. The SVR of patients in both treatment groups in our study are comparable to the SVR in prior studies employing the longer treatment duration of 48-52 weeks.

In our study, in the subset of patients with HCV RNA level at week 4, RVR was associated with a higher rate of SVR. Previous studies have noted the positive predictive value of RVR to predict SVR in patients with other genotypes.[19,26-30] However, we must caution that a sizable number of patients did not have RVRs measured during this study and this was not a prespecified outcome in our study, so we cannot conclude definitively what is the effect size of RVR on SVR in genotype 6. In addition, a small number of patients who did not attain RVR did go on to achieve SVR. Additional studies are needed to examine the effect of RVR on SVR in patients with HCV genotype 6.

In patients with HCV genotype 1, failure to achieve EVR is associated with failure to achieve SVR.[3] In our study we did not show that EVR was a predictor of SVR. This finding is due in part to the small sample size, reflected in the wide confidence interval, and the finding that only two patients in our study did not achieve EVR. Of note, one of these two patients went on to achieve SVR. In patients with HCV genotype 6, Fung et al. also found that EVR was not a reliable negative predictor of SVR, as in their sample of patients, three out of four patients (75%) who had not achieved EVR also did go on to achieve SVR.

Treatment adherence defined as completion of at least 75% of the intended dosage for at least 75% of the intended duration was lower in the 24-week group compared to the 48-week group (63% versus 79%), although this did not reach statistical significance ($P = 0.18$). A few observations may explain this discrepancy. Because the overall sample size is small, even a small number of events can significantly impact overall adherence. For example, 22% of patients in the 24-week group and 18% in the 48-week group were discontinued from the study, with serious AEs accounting for four cases the 24-week group compared to two in the 48-week group. However, the overall study adherence was high, as only two patients in the 24-week treatment group and three patients in the 48-week therapy group had to be withdrawn from the study due to failure to adhere to study protocol rather than serious AEs or nonresponse to therapy. In addition, as our study was an open-label study, it is possible that patients and providers were influenced by knowledge of patients' assigned treatment duration. Despite these limitations, this remains the only randomized and largest study of HCV genotype 6 treatment outcomes.

In conclusion, treatment with PEG IFN and RBV for 24 and 48 weeks resulted in a similar and high rate of SVR in patients with HCV genotype 6. Although SVR was greater in patients with HCV genotype 6 treated with PEG IFN for 48 weeks, treatment with 24 weeks was not statistically inferior to 48 weeks of treatment in our study. Patients treated for 48 weeks required more erythropoetin for anemia compared to patients treated for 24 weeks. Combination therapy with PEG IFN-α2a and RBV for 24 weeks for HCV genotype 6 may be acceptable for patients who cannot tolerate 48 weeks of therapy.

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