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ORIGINAL CONTRIBUTIONS

Liver and Biliary Tract

Higher Rate of Sustained Virologic Response in Chronic Hepatitis C Genotype 6 Treated With 48 Weeks *Versus* 24 Weeks of Peginterferon Plus Ribavirin

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OBJECTIVES: Infection with hepatitis C virus (HCV) genotype 6 is common in patients from parts of China and Southeast Asia. No study to date has examined the treatment response to peginterferon and ribavirin (PEG IFN + RBV) in these patients, or the effects of treatment duration on sustained virologic response (SVR) rates.

METHODS: We performed a retrospective study of 190 consecutive Asian-American patients who were diagnosed with HCV genotype 6 at a gastroenterology clinic in northern California between 2001 and 2004, 66 of whom were treatment-naïve and subsequently completed 24 wk of IFN + RBV or PEG IFN + RBV or 48 wk of PEG IFN + RBV therapy. The primary outcome was SVR.

RESULTS: There was no statistical difference in SVR of 31 patients treated with 24 wk of IFN + RBV and in 23 patients treated with 24 wk of PEG IFN + RBV (51.6% *vs* 39%, $P = 0.363$). The SVR in 12 patients treated with 48 wk of PEG IFN + RBV was significantly higher than that in those treated for only 24 wk (75% *vs* 39%, $P = 0.044$).

CONCLUSIONS: Treatment-eligible patients with HCV genotype 6 should be treated with a full course of 48 wk as tolerated. Larger prospective studies of patients with HCV genotype 6 are needed to confirm the optimal treatment duration with PEG IFN + RBV.

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INTRODUCTION

Infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is a major cause of morbidity and mortality in Asian patients worldwide. While HBV has long been recognized as a major cause of premature morbidity and mortality among Asian Americans, HCV has often been underappreciated in these patients despite a higher disease prevalence (3%) than the overall U.S. prevalence of 1.8% for HCV infection (1, 2). HCV is especially common among individuals originating from Southeast Asia, an area with a more severe hepatitis disease burden than that in the rest of Asia (5.6% in Thailand and 6.1% in Vietnam) (2). Moreover, a large number of these patients have been found to be infected with the lesser known HCV genotype 6 and its subtypes (also known as genotypes 7, 8, and 9) (3–6). Data from Hong Kong, Vietnam, and immigrants from such areas living in the United States show that approximately one-third of these HCV-infected patients have genotype 6 or one of its subtypes (7–10).

The current standard of care is to treat HCV-infected patients with a combination therapy of peginterferon (PEG IFN) and ribavirin (RBV) for 48 wk for those with genotype 1, and 24 wk for those with genotypes 2 and 3 (11–13). Patients with genotype 6 and its subtypes should also be treated with a combination therapy using PEG IFN + RBV, which has been shown to lead to a higher rate of sustained virologic response (SVR) in HCV-infected patients overall, as compared with a combination of standard IFN + RBV. However, the optimal treatment duration (*i.e.*, 24 wk *vs* 48 wk) is not known. Treatment with the longer 48-wk regimen may lead to a higher rate of SVR; on the other hand, treatment with the 24-wk regimen may also lead to a similar SVR rate, as in the case of patients with genotypes 2 and 3. If the latter is true, major benefits can be expected in terms of tolerability, reduction in adverse

events, as well as costs. Reduction in both direct costs (from costs of drugs, laboratory monitoring, and medical services) and indirect costs (from loss of work productivity in treated patients) can be expected if SVR following 24 and 48 wk of therapy are similar.

Unfortunately, data from large studies on the treatment tolerability and outcomes of HCV-infected Asian patients are currently lacking, even though racial differences in response to antiviral therapy for HCV infection have already been reported for whites and African Americans (14–17). In fact, there are no published studies to date evaluating the efficacy of PEG IFN in patients with genotype 6 and its subtypes, and none evaluating the different treatment durations. Our study examines outcomes in patients infected with HCV genotype 6 and its subtypes treated with a combination therapy including PEG IFN, and for varying durations at a U.S. clinic, the majority of whom are members of the growing Southeast Asian population in the United States, and for whom the burden of hepatitis C is substantial.

MATERIALS AND METHODS

Study Design and Patient Population

We performed a retrospective cohort study on all patients who were found to carry HCV genotype 6 and its subtypes via electronic medical records at a gastroenterology clinic between 2001 and 2004. Patients were identified using an electronic query that included a diagnosis of hepatitis C and results of HCV genotype testing. HCV genotype testing was performed by Quest Diagnostics, San Juan Capistrano, CA. Treatment criteria included detectable HCV ribonucleic acid polymerase chain reaction (RNA PCR) test level (lower detection limit 50 IU/mL or 160 copies/mL), persistently elevated alanine aminotransferase (ALT), and presence of hepatic fibrosis on biopsy. Treatment exclusion criteria included coinfection with HBV or human immunodeficiency virus, normal ALT (18, 19), absence of significant fibrosis on hepatic histology (19), decompensated liver disease, and severe comorbid conditions, such as significant cardiac disease. Treatments utilized were either standard IFN + RBV for 24 wk or PEG IFN + RBV for 24 wk and 48 wk. The choice of the different treatment regimens and duration above is largely due to timing, with the earliest patients being treated with IFN + RBV for 24 wk with the assumption that HCV genotype 6 may be easier to treat than genotype 1. With the approval of PEG IFN + RBV by the U.S. Food and Drug Administration, PEG IFN + RBV replaced IFN + RBV as the combination of choice. The clinical practice changed to extend the treatment course to 48 wk after anecdotal observation of a high relapse rate among treated patients with genotype 6 (20). Dosing regimens for the various groups are as follows: (a) IFN alfa-2b, 3 million units subcutaneously three times a week, and RBV 1,000 mg/day orally in divided doses; (b) weight-based PEG IFN alfa-2b, 80-150 μg subcutaneously + weight-based RBV 800–1,200 mg/day orally in divided doses; or (c) PEG IFN alfa-2a, 180 μg subcutaneously once a week + RBV orally 1,000–1,200 mg/day in divided doses.

This study was approved by administrative panels on Human Subjects on Medical Research at Stanford University.

Data Collection and Outcome Measurements

All patient data were obtained via review of existing medical records using a case report form that included various patient characteristics and treatment history. The primary end point of this study was SVR defined as undetectable HCV RNA PCR at 6 months following the end of the treatment in patients treated with PEG IFN + RBV. The secondary end point was end-of-treatment response (ETR) defined as undetectable HCV RNA PCR at the end of the treatment period.

Statistical Analysis

We used the Student's *t*-test or χ^2 statistics to compare patient characteristics and treatment outcomes among patient groups as appropriate. Statistical significance was defined as a 2-sided *P* value of 0.05 or less. All statistical analysis was performed using Stata version 7.0 (Stata Corporation, College Station, TX).

RESULTS

We identified 190 consecutive patients, who were diagnosed with genotype 6 and its subtypes between 2001 and 2004 in a gastroenterology clinic in the San Francisco Bay area. All of these patients were Asian. Of 190 patients, 69 did not receive treatment due to various reasons (Fig. 1). The majority of these 69 untreated patients either had no major indications for treatment (normal ALT or minimal fibrosis on liver biopsies, N = 27 or 39%) or had medical contraindications to treatment with IFN + RBV (N = 17 or 25%).

Of the 121 patients who received the combination therapy, 16 (13%) had prior treatment failure with IFN monotherapy and were excluded from the study analysis (Fig. 2). Of the remaining 105 treatment-naïve patients, 13.3% did not complete treatment and 21.9% were lost to follow-up and were excluded from the study analysis. We also excluded two patients who received 48 wk of IFN + RBV from the study analysis due to the small number of patients in this group.

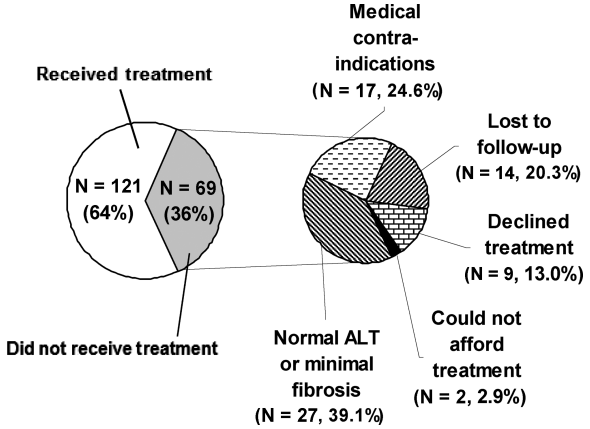

Figure 1. Distribution of 190 patients with HCV genotype 6 and reasons for no antiviral therapy.

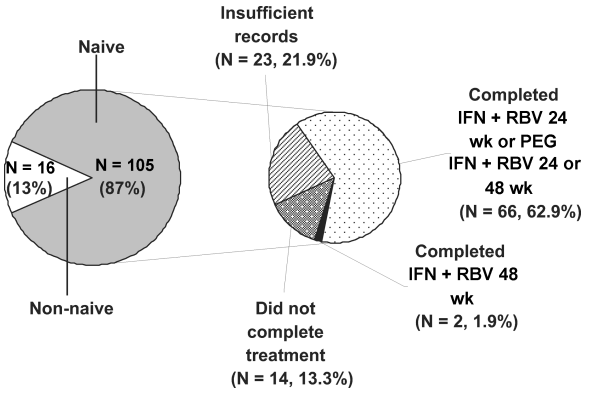

Figure 2. Treatment distribution of 121 HCV genotype 6 patients who underwent interferon (IFN)-based therapy with or without ribavirin (RBV).

In total, we included 66 patients for the study analysis: (a) 31 patients who completed 24 wk of IFN + RBV, (b) 23 patients who completed 24 wk of PEG IFN + RBV, and (c) 12 patients who completed 48 wk of PEG IFN + RBV. One patient receiving IFN + RBV and one in the PEG IFN + RBV 24-wk group had a reduction in IFN or PEG IFN dose due to significant neutropenia, and one in the IFN + RBV group also had a dose reduction due to general fatigue. None of these 66 patients received growth factors.

The mean age of patients who were treated with IFN + RBV was 50 ± 10 yr, and 71% were men. Four patients were thought to have cirrhosis based on the presence of coarse liver on ultrasound. The average weight was 63 ± 10 kg. The pretreatment mean ALT level was 97 ± 54 U/L, and the pretreatment mean HCV RNA PCR was 1.30 ± 1.18 million copies/mL. ETR for this group was 81.5%, and SVR was 51.6%. There was no statistically significant difference in the SVR of patients treated with IFN + RBV and PEG IFN + RBV for the same duration of 24 wk (51.6% *vs* 39%, $P = 0.363$).

Baseline characteristics of patients who were treated with PEG IFN + RBV are shown in Table 1. There were no statistically significant differences in age, gender, weight, and pretreatment ALT or HCV RNA PCR levels between the PEG IFN + RBV 24-wk and 48-wk groups. Treatment outcomes in these two groups are shown in Figure 3. There is a trend for higher ETR in the 48-wk group, but this was not statistically significant. However, SVR was significantly higher in patients treated for 48 wk (75%) compared with those treated for only 24 wk (39%). Among all patients treated for 24 wk (N = 44), there was a trend for a lower SVR rate in patients with cirrhosis compared with those without cirrhosis: 24.3% *versus* 51.4%, $P = 0.071$. The sample size of the 48-wk group was too small for a similar comparison. We did not find any significant differences in the SVR rate of patients with the main genotype 6 and those with its subtypes (previously classified as genotypes 7, 8, and 9, and their subtypes are as follows: 44.0% *vs* 48.3%, $P = 0.75$ for the 24-wk group [N = 25 and 29] and 75% for both genotype groups treated for 48 wk [N = 12]). All patients treated with IFN + RBV in this study were given 1,000 mg of RBV per day (1,000 mg for <75 kg and 1,200 mg if >75 kg as per the manufacturer's weight-based dosing), while 11 of 23 patients treated with PEG IFN + RBV for 24 wk were given only 800 mg of RBV per day (also as per weight-based dosing for this product: 800 mg a day for <65 kg). The SVR rate for patients treated for 24 wk with PEG IFN + RBV 1,000 mg or higher was 50.0% compared with 27.3% in those given RBV 800 mg per day ($P = 0.265$). We also noted similar trends among the 48-wk group given RBV 1,000 mg per day *versus* 800 mg or more: SVR = 83.3% *versus* 66.7%, $P = 0.505$. Only four patients in our study were treated with PEG IFN alfa-2a (3 for 24 wk and 1 for 48 wk).

DISCUSSION

Chronic hepatitis C is a significant disease in several geographic areas where the lesser known HCV genotype 6 is prevalent (9). Of the 169.7 million individuals infected with HCV worldwide, 62.2 million are from western Pacific countries and 32.3 million are from Southeast Asia (2). In parts of China and Southeast Asia, approximately one-third of patients with chronic hepatitis C have genotype 6 (9). However, little is known of the clinical characteristics of these patients, including their response to standard antiviral therapy.

Our study examines the clinical outcomes of patients with the HCV genotype 6 treated the with PEG IFN + RBV combination, and also includes the largest treatment cohort of HCV

Table 1. Baseline Characteristics of Treatment-Naïve HCV Genotype 6 Patients Who Received Peginterferon and Ribavirin (PEG IFN + RBV) for 24 and 48 Wk

Patient Characteristic (Mean ± SD or %)	PEG IFN + RBV 24 Wk (N = 23)	PEG IFN + RBV 48 Wk (N = 12)	*P* Value
Age (yr)	49 ± 10	50 ± 10	0.81
Male	69.6%	58.3%	0.51
Weight (kg)	64.0 ± 11.4	65.9 ± 16.8	0.75
Pretreatment ALT (U/L)	89 ± 46	101 ± 67	0.55
Pretreatment RNA (copies/mL)	$1.95 \times 10^6 \pm 4.4 \times 10^5$	$1.57 \times 10^6 \pm 4.5 \times 10^5$	0.57
Pretreatment liver biopsy			
Stage	1.73 ± 1.01	2.4 ± 1.14	0.23
Grade	2.09 ± 0.83	2.2 ± 1.10	0.83

SD = standard deviation; ALT = alanine aminotransferase.

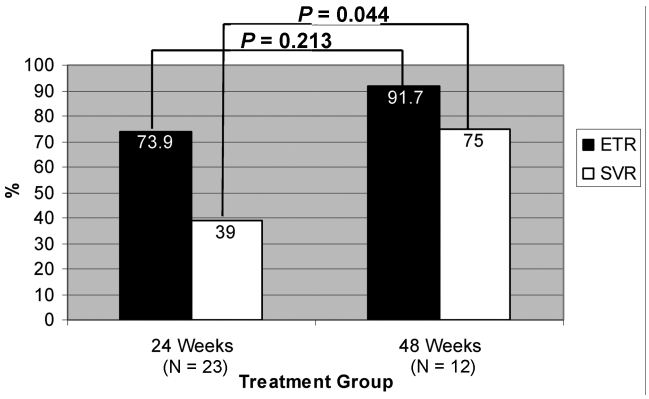

Figure 3. End-of-treatment response (ETR) and sustained virologic response (SVR) in HCV genotype 6 patients who completed 24 wk *versus* 48 wk of therapy with peginterferon and ribavirin (PEG IFN + RBV).

genotype 6 patients. We observed a significantly higher SVR rate for patients treated with PEG IFN + RBV for 48 wk compared with those treated for only 24 wk (75% *vs* 39%, $P = 0.044$). The off-treatment relapse rate to PEG IFN + RBV was 35% for the 24-wk group compared with 17% for the 48-wk group. Among patients treated for 24 wk, we observed a higher SVR rate for patients treated with IFN + RBV compared with PEG IFN (51.6% *vs* 39.0%). Though this difference was not statistically significant, it may represent a significant clinical trend that, in this case, may be due the higher weight-based dose of RBV given with the IFN + RBV regimen, as suggested by the trend for an increased SVR rate in patients given the higher RBV dose between both PEG IFN groups (24 wk: SVR 50.0% *vs* 27.3%, $P = 0.265$; 48 wk: SVR 83.3% *vs* 66.7%, $P = 0.505$).

Prior studies on this topic only include patients treated with standard IFN + RBV, and all of these patients were treated for 52 wk. Hui and colleagues reported SVR rates of 62.5% for 16 patients with HCV genotype 6 and 29.0% for 24 patients with HCV genotype 1 included in their study (21). Patients in this study were treated with 3 million units of IFN and weight-based RBV for a total of 52 wk. The observed SVR rate for HCV genotype 6 patients treated with IFN + RBV for 52 wk in this study is higher than what we observed for both our IFN + RBV and PEG IFN + RBV groups who were treated for only 24 wk, though it appears to be lower than our observed SVR rate of 75% for those treated with PEG IFN + RBV for the longer duration of 48 wk.

Dev and colleagues studied treatment response in their retrospective study of 40 HCV genotype 6 and 13 HCV genotype 1 Asian patients living in Australia (22). They reported SVR rates of 82.5% in patients with HCV genotype 6 and 62.0% in patients with HCV genotype 1. Patients in this study were first treated with an induction dose of IFN of 5 million units daily for 8 wk, followed by the standard dose of 3 million units three times a week and RBV 1,000–1,200 per mg day. The SVR rate for HCV genotype 6 patients treated with IFN + RBV for 52 wk in this study is higher than what we observed, even for patients treated with 48 wk of PEG IFN + RBV. However, the SVR rate reported for patients with HCV genotype 1 in Dev *et al.*'s study is also higher than that reported in the pivotal trials for both the IFN + RBV and PEG IFN + RBV combinations (11, 13, 23). It is not clear whether the practice of IFN induction in the first 8 wk and/or the higher dose of RBV used contribute to the higher-than-expected SVR in both patient groups in this study.

As with the study by Dev and colleagues above, our study was also a retrospective study, which is its main limitation. The primary outcome, however, is the SVR rate, which is an objective measurement. In addition, we did not use intention-to-treat because it may grossly underestimate the SVR rate, as patient follow-up and SVR data availability would be expected to be poorer than those obtained from studies with prospective follow-up of patients. Patients in all three study groups completed either 24 or 48 wk of their assigned treatment. Nevertheless, this is the largest series examining treatment response in patients with chronic hepatitis C genotype 6 ($N = 66$), and the only one to date that included PEG IFN and at varying durations. The disease burden of chronic hepatitis C genotype 6 is substantial in China and Southeast Asia, and in Asian-American immigrants from such areas, an immigrant group with one of the most rapidly rising censuses in the United States.

In conclusion, an association between longer therapy and a higher SVR rate appears to exist for patients treated with PEG IFN + RBV for 48 wk (compared with 24 wk). There are no statistically significant differences in the SVR rates of patients treated with 24 wk of IFN + RBV or PEG IFN + RBV. Larger and prospective studies are needed to confirm these observations, and until further data are available, patients with HCV genotype 6 should be treated with PEG IFN + RBV for 48 wk.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Chronic hepatitis C is very prevalent in Southeast Asia (~6%), parts of China, and in Asian-American immigrants from such areas.
- Approximately one-third of these patients with hepatitis C virus (HCV) have genotype 6.
- No studies to date examined response to the peginterferon and ribavirin (PEG IFN + RBV) combination or a shorter treatment duration in HCV genotype 6.

What Is New Here

- HCV genotype 6 patients may have sustained virologic response rates comparable with those reported for genotype 2 or 3 if treated with PEG IFN + RBV for 48 wk.
- Relapses are much more common in HCV genotype 6 patients treated for 24 wk compared with those treated for 48 wk.

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CONFLICT OF INTEREST

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