MAJOR ARTICLE

Chronic Hepatitis C Virus Genotype 6 Infection: Response to Pegylated Interferon and Ribavirin

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Background. To date, no study has evaluated pegylated interferon for the treatment of chronic infection with hepatitis C virus (HCV) genotype 6. We aimed to determine the efficacy of pegylated interferon plus ribavirin for treating infection with genotype 6 versus genotype 1.

Methods. Forty-two patients chronically infected with HCV (for genotype 1, $n = 21$; for genotype 6, $n = 21$) were treated with pegylated interferon α-2a ($n = 20$) or α-2b ($n = 22$) combined with oral ribavirin for 48 weeks.

Results. There was no difference between genotypes 1 and 6 in the rates of early virological response (76% vs. 81%; $P > .05$) and end-of-treatment response (71% vs. 81%; $P > .05$). Patients infected with genotype 6 had a higher rate of sustained virological response (SVR) than did patients infected with genotype 1 (86% vs. 52%; $P = .019$). The overall adverse-effects profile was similar in both genotype groups. There was no significant difference in the rate of SVR between patients receiving pegylated interferon α-2a and those receiving α-2b. Multivariate analysis showed that genotype was the only significant factor associated with SVR ($P = .039$).

Conclusions. Treatment with pegylated interferon and ribavirin for 48 weeks resulted in a significantly higher rate of SVR in patients infected with genotype 6 than in those infected with genotype 1. Further studies are required to determine whether lower dosages and 24 weeks of therapy may be sufficient for the treatment of genotype 6 infection.

Approximately 175 million people worldwide are chronically infected with hepatitis C virus (HCV), accounting for the majority of cases of liver cirrhosis and hepatocellular carcinoma in Western populations [1]. Up to 4 million persons are newly infected each year, of which some 50%–85% will progress to chronic infection [2]. Currently, there are 6 recognized major HCV genotypes, each having a distinct and different geographical distribution [3]. The predominant genotypes found in Western populations are 1, 2, and 3, at varying frequencies [4–6]. Genotype 4 is found commonly in North Africa and the Middle East [7], whereas genotype 5 is found predominantly in South Africa [8].

In Hong Kong, the major HCV genotypes are 1 and 6, with a prevalence rate of 65% and 27%, respectively, in patients with chronic hepatitis C [9]. The prevalence of genotype 6 infection is higher in certain subgroups, including those with thalassemia and injection drug users (50% and 60% of chronic HCV infections, respectively) [10]. Because HCV genotype 6 is predominantly found only in Hong Kong, southern China, Taiwan, and other parts of Southeast Asia, limited data on its response to treatment are available.

A previous study of 61 Southeast Asian patients receiving standard interferon α-2b at a dosage of 5 MU/day for 8 weeks followed by 3 MU thrice weekly for 44 weeks combined with ribavirin showed the rate of sustained virological response (SVR) in patients with genotype 6 infection to be 100%, compared with 62% in patients with genotype 1 infection [11]; however, this promising figure was derived from only 7 patients infected with genotype 6a. Another study of 40 patients in Hong Kong treated with standard interferon α-2b at 5 MU thrice weekly for 12 months combined with ribavirin showed a better rate of SVR for genotype 6 than for genotype 1 (63% vs. 29%; $P = .04$) [12].

The available results suggest that response to antiviral therapy in patients infected with HCV genotype 6 is similar to that in patients infected with genotype 2 or 3 and is superior to that in patients infected with genotype 1.

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Table 1. Baseline demographic and laboratory data.

Parameter	Genotype 1 ($n = 21$)	Genotype 6 ($n = 21$)	P
Age, years	52 (30–63)	49.5 (14–64)	.571
Male, no. (%)	12 (57)	11 (52)	.757
Weight, kg	61 (47–81)	62 (44–100)	.940
Bilirubin level, μmol/L	12 (2–21)	11 (5–18)	.686
ALT level, U/L	121 (44–382)	138 (27–226)	.358
Albumin level, g/L	43 (33–47)	42 (37–48)	.742
Hemoglobin level, g/L	144 (105–174)	145 (104–161)	.960
Leukocyte count, 10^9 cells/L	5.4 (3.6–7.7)	5.7 (2.9–7.9)	.632
Platelet count, 10^9 cells/L	204 (84–303)	173 (73–372)	.365
HCV RNA level, IU/mL	474,000 (7500–144,9450)	722,000 (4808–5,176,890)	.421
Cirrhosis (ultrasound), no. (%)	3 (14)	6 (29)	.226

NOTE. Data are median (range) values, unless otherwise specified. ALT, alanine aminotransferase; HCV, hepatitis C virus.

For genotypes 1, 2, and 3, the rates of SVR have been further improved by the use of pegylated interferon, although there has been no report on the use of pegylated interferon in patients infected with genotype 6. The aim of the present study was to determine the efficacy of pegylated interferon plus ribavirin for the treatment of chronic infection with HCV genotype 6 compared with genotype 1.

METHODS

Patients. All patients infected with chronic HCV genotype 1 or 6 between February 2003 and February 2006 and treated with combination pegylated interferon and ribavirin at the hepatitis clinic at Queen Mary Hospital, Hong Kong, were included in this study. Patients with hepatitis B virus or HIV coinfection were excluded, as were patients with recurrent HCV infection after liver transplantation. In addition, patients who had previously received conventional interferon treatment were excluded. Patients recruited in the study were seropositive for anti-HCV by microparticle enzyme immunoassay (Abbott AxSYM; Abbot Laboratories) and were positive for HCV RNA by polymerase chain reaction (Cobas TaqMan HCV; Roche Molecular Systems). HCV genotypes were determined using the Linear Array Detection Kit (Roche Molecular Systems) in accordance with the manufacturer's instructions, which allows the determination of HCV genotypes 1 to 6.

Patients were treated with either pegylated interferon α-2a (Pegasys; Roche) or pegylated interferon α-2b (Pegintron; Schering-Plough) in combination with oral ribavirin for 12 months. Among patients receiving pegylated interferon α-2a, ribavirin was given at a daily dose of 1000 and 1200 mg for those weighing <75 and ≥ 75 kg, respectively. Among patients receiving pegylated interferon α-2b, ribavirin was given at a daily dose of 800, 1000, and 1200 mg for those weighting <65 kg, 65–85 kg, and >85 kg, respectively. Pegylated interferon α-2a was given at a dosage of 180 μg/week subcutaneously, and pegylated interferon α-2b was given at a dosage of 1.5 μg/kg/week.

Patients were followed up monthly with liver biochemistry analysis, complete blood counts, and thyroid function tests. Clinical adverse effects due to interferon and ribavirin were also monitored during each visit. HCV RNA level was checked at baseline, at week 12 for determination of early virological response (EVR), at the completion of treatment for determination of end-of-treatment response (EOTR), and at 6 months after the completion of treatment for determination of SVR.

Statistics. All statistical analyses were performed using SPSS (version 14.0). Categorical variables were analyzed using the χ^2 test or Fisher's exact test as appropriate. Continuous variables with a skewed distribution were analyzed using the Mann-Whitney U test. The results were analyzed on an intention-to-treat basis. Multivariate analysis was performed using binary logistic regression. $P \leq .05$ was considered to indicate statistical significance.

RESULTS

Treatment and baseline data. In total, 42 patients chronically infected with HCV genotype 1 ($n = 21$) or 6 ($n = 21$) received treatment with combination pegylated interferon and ribavirin between February 2003 and February 2006. Thirty-five patients (83%) presumably acquired their HCV infection from blood transfusions done before the introduction of screening for HCV in 1991. Three patients (7%) had a history of injection drug use, and 4 (10%) had neither a history of injection drug use nor previous blood transfusions. The baseline demographic and laboratory data are shown in table 1. The patients were well matched with respect to age, sex, weight, and baseline laboratory parameters (including HCV load and presence of cirrhotic changes on ultrasound) between the 2 genotype groups.

Twenty patients (48%) were treated with pegylated interferon α-2a, and 22 (52%) were treated with pegylated interferon α-2b.

Table 2. Treatment characteristics.

Parameter	Genotype 1	Genotype 6	*P*
Pegylated interferon			
Dose of α-2a, μg	180	180	1.000
Dose of α-2b, μg	90 (70–100)	80 (60–120)	.270
Dose reduction, no. (%)	2 (11)	6 (40)	.100
Ribavirin			
Dose, mg	1000 (800–1200)	1000 (800–1200)	.233
Dose reduction, no. (%)	10 (53)	6 (40)	.464

NOTE. Doses are expressed as median (range) values.

There was no significant difference in the types of interferon used between genotypes 1 and 6 ($P = 1.000$). Eight patients (19%) had treatment stopped prematurely secondary to adverse effects, and the remaining 34 (81%) completed 48 weeks of treatment. There was no significant difference in the rates of patients stopping treatment prematurely between genotypes 1 and 6 (10% vs. 29%; $P = .238$).

Of the patients who completed 48 weeks of treatment, 2 (11%) with genotype 1 infection required a reduction in the dose of interferon, compared with 6 patients (40%) with genotype 6 infection ($P = .100$). Ten patients (53%) with genotype 1 infection required a reduction in the dose of ribavirin, compared with 6 patients (40%) with genotype 6 infection ($P = .464$). The treatment characteristics are summarized in table 2.

Virological response. Comparison of the virological response to combined pegylated interferon and ribavirin therapy between genotypes 1 and 6 is summarized in figure 1. There was no significant difference in the rates of EVR (as defined by an undetectable HCV RNA level at week 12) and EOTR (as defined by an undetectable HCV RNA level at the end of treatment) between patients infected with genotype 1 and those infected with genotype 6. Patients infected with genotype 6, however, had a significantly higher rate of SVR than did those infected with genotype 1 (86% vs. 52%; $P = .019$).

Of the patients with genotype 1 infection, 16 (76%) achieved an EVR, of whom 10 (63% of those with an EVR) went on to achieve a SVR; in contrast, of the 5 patients (24%) with genotype 1 infection who did not achieve an EVR, only 1 (20% of those without an EVR) went on to achieve a SVR. Of the patients with genotype 6 infection, 17 (81%) achieved an EVR, of whom 15 (88% of those with an EVR) achieved a SVR; of the 4 patients (19%) with genotype 6 infection who did not achieve an EVR, 3 (75%) went on to achieve a SVR.

Therapy was stopped prematurely in 6 patients infected with genotype 6, after 2, 24, 24, 24, 28, and 44 weeks. Of these 6 patients, 4 (67%) went on to achieve a SVR. These 4 patients had been treated for 24, 24, 28, and 44 weeks, and all had achieved an EVR. Of those patients with genotype 6 infection who completed 48 weeks of therapy, only 1 did not achieve a SVR. He was a 64-year-old man with underlying cirrhosis whose dose of pegylated interferon was halved at week 12 because of significant neutropenia; he then had treatment withheld for 2 weeks and was subsequently treated with half doses of pegylated interferon and ribavirin.

There was no significant difference in the rate of SVR between patients treated with pegylated interferon α-2a and those treated with pegylated interferon α-2b, regardless of whether they were infected with genotype 1 (60% vs. 45%; $P = .670$) or genotype 6 (100% vs. 82%; $P = .289$).

All but 1 patient who achieved a SVR in both genotype groups had a normal alanine aminotransferase (ALT) level 6 months after the completion of therapy. The single patient with a SVR who did not have a normal ALT level at 6 months had developed hepatocellular carcinoma, which was diagnosed at the end of treatment.

Multivariate analysis using binary logistic regression was performed on demographic factors and baseline laboratory parameters, including age, sex, ALT level, platelet count, albumin level, presence of cirrhosis, viral load, genotype, and type of pegylated interferon used. Of these factors, only genotype was significantly associated with SVR ($P = .039$).

Safety. Of the 42 patients included in the analysis, 34 (81%) completed 48 weeks of therapy. Eight patients (19%) had premature termination of their treatment because of significant adverse effects, including generalized rash, severe thrombocytopenia, and thyrotoxicosis. The adverse-effects profile is summarized in table 3. There was no significant difference in the adverse-effects profile between patients infected with genotype 1 and those infected with genotype 6.

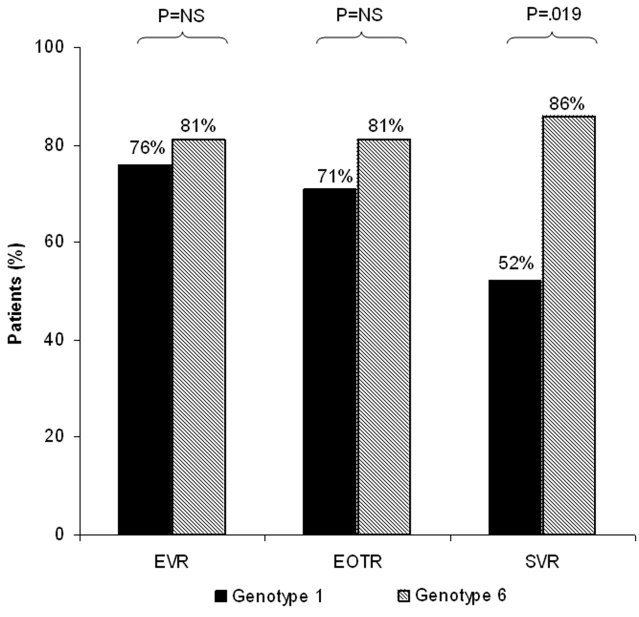

Figure 1. Virological response to treatment. EOTR, end-of-treatment response; EVR, early virological response; NS, not significant; SVR, sustained virological response.

Table 3. Adverse effects due to treatment.

Adverse effect	Genotype 1	Genotype 6	*P*
Rash	5 (24)	7 (33)	.495
Anemia[a]	10 (48)	6 (29)	.204
Neutropenia[b]	1 (5)	4 (19)	.343
Thrombocytopenia[b]	1 (5)	0 (0)	1.000
Insomnia	3 (14)	0 (0)	.232
Thyrotoxicosis[b]	0 (0)	2 (10)	.488

NOTE. Data are no. (%) of patients.

[a] Requiring a reduction in the dose of ribavirin.

[b] Requiring a reduction in the dose or termination of interferon.

The most common adverse effect in both genotype groups was anemia requiring a reduction in the dose of ribavirin. Hemoglobin level returned to normal in the majority of patients 6 months after the completion of treatment; 1 patient had persistent anemia due to menorrhagia.

Of the 34 patients who completed 48 weeks of treatment, 8 (24%) required a reduction in their dose of interferon; there was no significant difference between patients infected with genotype 1 and those infected with genotype 6. Sixteen patients (47%) required a reduction in their dose of ribavirin. Doses and differences between patients infected with genotype 1 and those infected with genotype 6 are summarized in table 2.

DISCUSSION

The current standard treatment for chronic hepatitis C is the combination of pegylated interferon and ribavirin. Several landmark studies have shown that HCV genotype 1 is associated with a less favorable response than genotype 2 or 3, with a SVR rate of ~50% versus 76%–82% [13–15]. Presently, a large proportion of the available data on the treatment of chronic HCV infection relates to genotypes 1, 2, and 3 because of its prevalence in North America and Europe, where large multicenter trials are conducted. As a result, there is a general paucity of data on treatment response in patients infected with other genotypes, including genotype 6.

Previous studies using standard interferon and ribavirin in patients with HCV genotype 6 infection showed a SVR rate of 63%–100%, suggesting that virological response for genotype 6 is similar to that for genotype 2 or 3 and is superior to that for genotype 1 [11, 12]. However, there has been no formal head-to-head study of pegylated interferon comparing efficacy between patients infected with genotype 1 and those infected with genotype 6. In the present study, we investigated the virological response in patients infected with HCV genotype 6 and treated with pegylated interferon and ribavirin, in comparison to the response in those infected with genotype 1. We showed a significantly higher rate of SVR in patients infected with genotype 6 than in those infected with genotype 1 (86% vs. 52%; $P = .019$). The patients in both groups were well matched with respect to age, sex, weight, baseline viral load, and liver biochemistry. The rate of SVR in patients with genotype 1 infection in this study is comparable to that observed in older, larger trials using pegylated interferon and ribavirin at the same doses [13, 14].

There were, however, no significant differences in the rates of EVR and EOTR between patients with genotype 1 infection and those with genotype 6 infection. This suggests that the difference in the rate of SVR was likely due to the higher rate of relapse in patients infected with genotype 1 (i.e., those who achieved an EOTR but subsequently became positive for HCV RNA after the cessation of treatment and therefore did not achieve a SVR). Of the patients with genotype 6 infection, 4 did not achieve an EVR, and 3 of these 4 achieved a SVR on follow-up, suggesting that EVR is not a reliable predictor of SVR in patients infected with HCV genotype 6. This is in contrast to genotype 1 infection, for which it has been shown that patients who do not achieve an EVR are less likely to achieve a SVR, and consideration should be given to cessation of therapy [13, 16, 17]. In the present study, only 1 of the 5 patients with genotype 1 infection who did not achieve an EVR went on to achieve a SVR.

In the present study, there was no difference in the rate of SVR between patients treated with pegylated interferon α-2a and those treated with α-2b. Of the patients with genotype 6 infection, 6 had premature discontinuation of therapy. Despite this, 4 (67%) went on to have a SVR.

One of the drawbacks of the present study is the determination of HCV genotype by means of linear array detection rather than the reference standard of direct sequencing. There is the potential for mistyping of genotype 6 subtypes (previously known as genotypes 7–9) as genotype 1. These subtypes are found mainly in Vietnam, Thailand, Myanmar (Burma), and Indonesia; the prevalence of these subtypes in Hong Kong remains unknown but is likely to be very low. In a population study of 1055 patients with chronic hepatitis C in Hong Kong, no genotype 6b, 6d, 6g, 6h, and 6k was identified, and the accuracy of the genotype method was confirmed by sequencing of the NS5A region [18]. Therefore, mistyping of genotype 6 subtypes in the present study is very unlikely.

In conclusion, treatment with pegylated interferon and ribavirin for 12 months resulted in a significantly higher rate of SVR in patients infected with genotype 6 (86%) than in those infected with genotype 1 (52%). Given the favorable response to treatment, further studies are required to determine whether a lower dosage and a shorter duration of therapy may be sufficient in patients with genotype 6 infection. Until such confirmatory data are available, patients infected with HCV genotype 6 should continue to receive 48 weeks of therapy.

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