JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2012, **19,** 423–430 doi:10.1111/j.1365-2893.2011.01566.x

Response-guided therapy for patients with hepatitis C virus genotype 6 infection: a pilot study

P. Tangkijvanich, [1] P. Komolmit, [2] V. Mahachai, [2] K. Poovorawan, [2] S. Akkarathamrongsin[3] and Y. Poovorawan[3] [1]*Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;* [2]*Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; and* [3]*Department of Pediatrics, Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Received July 2011; accepted for publication October 2011

SUMMARY. The optimal duration of treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) in patients with hepatitis C virus (HCV) genotype 6 is unknown. This study was aimed at determining treatment response on the basis of rapid virological response (RVR) of HCV genotype 6 in comparison with genotypes 1 and 3. Sixty-six treatment naïve patients were treated with PEG-IFN-α2a (180 μg/week) plus weight-based RBV (1000–1200 mg/day). Patients with genotype 1 (n = 16) and genotype 3 (n = 16) were treated for a fixed duration of 48 and 24 weeks, respectively. Patients with genotype 6 (n = 34) who achieved RVR were treated for 24 weeks (response-guided therapy) and the remaining patients were treated for 48 weeks (standard therapy). The mean baseline HCV RNA levels were not statistically different between groups (6.4 ± 0.8, 6.0 ± 1.0 and 6.5 ± 0.8 Log_{10} IU/mL for genotypes 1, 3 and 6, respectively). Patients with genotypes 1, 3 and 6 achieved RVR in 43.8%, 87.5% and 73.5% of cases, respectively. One patient with genotype 1 and 3 with genotype 6 were considered nonresponders and discontinued therapy. Sustained virological response (SVR) was achieved in 62.5%, 81.3% and 76.5% of patients with genotypes 1, 3 and 6, respectively. The SVR rate in patients with genotype 6 who underwent response-guided therapy was 88%. This pilot study suggested that the SVR rate of HCV genotype 6 was at an intermediate level between those of genotypes 3 and 1. Treatment with PEG-IFN plus RBV for 24 weeks may be sufficient for patients with genotype 6 who achieve RVR. Prospective randomized trials are required to evaluate this response-guided strategy in a larger number of patients with genotype 6.

Keywords: hepatitis C, genotype 6, treatment duration, virological response, RVR.

INTRODUCTION

Hepatitis C virus (HCV) infection is a worldwide public health problem, with an estimated 170 million people infected with the virus [1]. HCV has been classified into six major genotypes and numerous subtypes, which display unique patterns of geographic distribution [2,3]. HCV genotypes 1–3 are distributed globally and account for the majority of HCV infections worldwide. HCV genotype 4 is predominantly found in the Middle East and North Africa, while genotype 5 is limited to South Africa. HCV genotype 6 is distributed primarily in south China and South-East Asia and displays pronounced genetic diversity [4]. In Thailand, approximately 2% of the general population have been chronically infected with HCV and the common genotypes are genotypes 3, 1 and 6, respectively [5,6].

The current standard therapy for patients with chronic HCV infection is a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) for 48 weeks for those with genotypes 1 and 4 and 24 weeks for those with genotypes 2 and 3 [7]. Prior limited studies have suggested that the response rate of HCV genotype 6 may be at an intermediate level between those of genotypes 3 and 1 [8–11]. However, the optimal treatment duration (24 *vs* 48 weeks) for genotype 6 is currently unknown. Previous retrospective studies showed that 48 weeks of combination therapy might be the optimal duration of treatment for genotype 6 [8,12]. However, recent prospective data demonstrated that a 24-week course of PEG-IFN plus RBV was sufficient for patients with

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; cEVR, complete early virological response; EVR, early virological response; HBV, hepatitis B virus; HCV, hepatitis C virus; pEVR, partial early virological response; RBV, ribavirin; RGT, response-guided therapy; RVR, rapid virological response; SVR, sustained virological response.

Correspondence: Pisit Tangkijvanich, MD, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
E-mail: pisittkvn@yahoo.com

genotype 6 and might not be statistically inferior to a 48-week duration of therapy [13].

Virological response kinetics during therapy have emerged as important prognostic factors of treatment outcome in patients with chronic HCV infection [7,14]. Absence of an early virological response (EVR) at week 12 during therapy is the best negative predictor for nonresponse to treatment. In contrast, rapid virological response (RVR; defined as undetectable HCV RNA at week 4) is regarded as the most important predictor for sustained virological response (SVR; defined as undetectable HCV RNA at week 24 after the end of therapy) and has emerged as an important milestone to guide the appropriate duration of therapy. In patients with genotype 1, an individualized approach to therapy designed according to early viral kinetics has been adopted to optimize therapeutic outcome in patients. Recent clinical trials have used RVR to identify those patients with low baseline viral load that may benefit from a shortened treatment duration of 24 weeks [15–17]. Taken together, these data suggest the feasibility of a response-guided therapy for patients with HCV genotype 6 based on the early viral kinetics. In this study, we conducted a pilot trial to individualize the duration of treatment (24 *vs* 48 weeks) in patients with HCV genotype 6 on the basis of RVR and compared SVR rates to those of patients with genotypes 1 and 3.

PATIENTS AND METHODS

Patients

Male and female patients aged 18–70 years with HCV genotypes 1, 3 and 6 infection who had not received antiviral therapy were eligible for enrolment and had to fulfil the following entry criteria: HCV RNA level more than 10 000 IU/mL; increased serum alanine aminotransferase (ALT) levels at screening and liver biopsy performed within 12 months preceding study enrolment confirming chronic hepatitis. Exclusion criteria were as follows: decompensated liver disease; hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection; other causes of liver disease; active injection drug use or alcohol dependence (self-reported intake, ≥40 g/day in women and ≥60 g/day in men); pregnancy or breast-feeding; serum creatinine level ≥1.5 mg/dL; haemoglobin concentration, <11 g/dL in women or <12 g/dL in men; neutrophil count, <1500 cells/mm^3; platelet count, <80 000 platelets/mm^3; a major psychiatric illness; seizure disorder; serious co-morbid conditions and evidence of malignant neoplastic diseases.

Study design

This pilot prospective study was conducted in a single tertiary hospital (King Chulalongkorn Memorial Hospital) in Bangkok, Thailand from May 2009 to April 2011. The protocol of the study had been approved by the Institutional Review Board, and all participants had provided written informed consent. The study followed the Helsinki Declaration and Good Clinical Practice guidelines. To compare the response rate of HCV genotype 6 with those of genotypes 1 and 3, patients infected with genotypes 1, 3 and 6 were enrolled on a 1:1:2 basis. All patients received PEG-IFN-α2a (Pegasys; Roche Pharmaceuticals, Bangkok, Thailand) 180 μg/week plus weight-based RBV (Copegus; Roche Pharmaceuticals) according to the following body weights: ≤75 kg, 1000 mg/day; and >75 kg, 1200 mg/day. Regarding treatment duration, patients infected with HCV genotype 1 (group 1) and HCV genotype 3 (group 3) were treated for a fixed duration of 48 and 24 weeks, respectively. Patients infected with HCV genotype 6 (group 6) who achieved RVR were assigned to treatment for 24 weeks [response-guided therapy (RGT)-group 6] and the remaining patients were treated for 48 weeks [standard therapy (ST)-group 6].

Patients with undetectable HCV RNA at week 12 were defined as having a complete early virological response (cEVR), whereas those with a minimum 2-log$_{10}$ decrease from the baseline in HCV RNA at week 12 were defined as having a partial early virological response (pEVR). Patients with no or minimal change in HCV RNA levels (<2-log$_{10}$ decrease from the baseline at week 12) were defined as nonresponders and therapy was discontinued. All patients who completed the treatment were followed up for an additional 24 weeks after the end of therapy to assess SVR.

Laboratory tests

HCV genotype was determined by nucleotide sequencing of the core and NS5B regions followed by phylogenetic analysis as described previously [5]. The levels of serum HCV RNA were assessed at baseline; at weeks 4, 12, 24, end-of-treatment and at 24 weeks of follow-up by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) (COBAS TaqMan HCV assay; Roche Diagnostics, Basel, Switzerland), in accordance with the manufacturer's instructions.

Assessment of efficacy

The primary efficacy end point was to achieve SVR, defined as undetectable HCV RNA 24 weeks after the end-of-treatment. Treatment failures were defined as follows: breakthrough (reappearance of HCV RNA during antiviral treatment period), relapse (reappearance of HCV RNA during follow-up period in patients with an end-of-treatment virological response), and nonresponse (a decrease in the HCV RNA level <2 log$_{10}$ after 12 weeks of treatment or detectable viral load at week 24), or discontinuation (treatment withdrawal for any reason). Secondary end points were to study the variables

associated with SVR and to investigate the efficacy of week 4 virological response to predict treatment outcome.

Assessment of safety

Safety was assessed through the monitoring of adverse events and laboratory tests at weeks 2, 4, 6 and 8 then monthly thereafter during treatment and at weeks 12 and 24 after therapy discontinuation. Any life-threatening adverse event prompted treatment withdrawal. Stepwise reduction of RBV dosage of 200 mg/day and reductions of PEG-IFN-α2a dose to 135 and 90 μg/week were permitted to manage adverse events or laboratory abnormalities. Hematopoietic growth factors for the management of significant haematological toxicity were not used in this study.

Statistical analysis

The rates of SVR in each group of patients were calculated on an intention-to-treat basis. The Mann–Whitney's *U* test or Student's test were used to compare continuous variables, and the χ^2 test or Fisher's exact test were used to compare categorical variables. Univariate and multivariate logistic regression analysis was used to assess odd ratios relating pretreatment variables and viral kinetics associated with SVR. $P < 0.05$ for a two-tailed test was considered statistically significant. All statistical analyses were performed using the SPSS software for Windows version 17.0 (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 66 patients were included in this pilot study. There were 16 patients in group 1, 16 patients in group 3 and 34 patients in group 6. Table 1 summarizes demographic and baseline characteristics of the patients by HCV genotypes. There were no significant differences in the baseline characteristics between each group in terms of gender distribution, mean age, body mass index (BMI), previous blood transfusion, ALT level, HCV RNA level and the degree of liver fibrosis assessed by histology. However, patients in group 6 had a significantly higher proportion of previous history of intravenous drug use compared with the other groups.

Virological response and treatment outcome

Of group 1, 14 (87.5%) patients completed the 48-week treatment and follow-up. One patient in this group was lost to follow up by week 24 during therapy. One patient showed minimal changes in HCV RNA levels at week 12 and therapy was discontinued because of nonresponse. Of group 3, all patients completed the 24-week treatment and follow-up. Of group 6, 25 (73.5%) patients who achieved RVR were assigned to treatment for 24 weeks (RGT-group 6) and the remaining 9 (26.5%) patients were assigned to treatment for 48 weeks (ST-group 6). All patients in RGT-group 6 completed the 24-week treatment and follow-up. Of ST-group 6, three patients were nonresponders and therapy was discontinued and the remaining 6 (66.7%) patients completed the 48-week treatment and follow-up (Fig. 1).

Figure 2 compares the virological response to the combined therapy within each group. RVR were achieved in 14 of 16 (87.5%) patients in group 3 and 25 of 34 (73.5%) patients in group 6, which was not of statistical significance ($P = 0.277$), but statistically more significant than that in group 1 (7 of 16 patients; 43.8%) ($P = 0.016$ and $P = 0.045$, respectively). The rates of cEVR were comparable between group 3 (15 of 16, 93.8%) and group 6 (30 of 34, 88.2%) ($P = 0.551$) and were higher than in group 1 (12 of 16 patients, 75%), although there was no significant difference ($P = 0.174$ and $P = 0.243$, respectively). The overall rate of SVR in group 3 (13 of 16 patients, 81.3%) was similar to that of group 6 (26 of 34 patients; 76.5%)

Table 1 Demographic and clinical baseline characteristics of the patients according to hepatitis C virus genotypes

Baseline characteristics	Genotype 1 ($n = 16$)	Genotype 3 ($n = 16$)	Genotype 6 ($n = 34$)	*P*
Age (yr)	46.4 ± 12.5	42.8 ± 8.2	41.2 ± 8.4	NS
Sex (male)	56.3%	81.3%	67.6%	NS
Body mass index (BMI) (kg/m^2)	23.4 ± 13.1	21.3 ± 5.7	23.7 ± 3.7	NS
Previous blood transfusion	50.0%	53.8%	33.3%	NS
Previous intravenous drug users	15.4%	23.1%	40.7%	0.041
ALT (U/L)	82.7 ± 57.5	82.6 ± 51.9	62.6 ± 54.5	NS
Log_{10} HCV RNA (IU/ml)	6.4 ± 0.8	6.0 ± 0.8	6.5 ± 0.8	NS
Liver fibrosis score				NS
Score 0–2	69.2%	66.7%	71.4%	
Score 3–4	30.8%	33.3%	28.6%	

ALT, alanine aminotransferase; Data described as means ± SD or proportions (%).

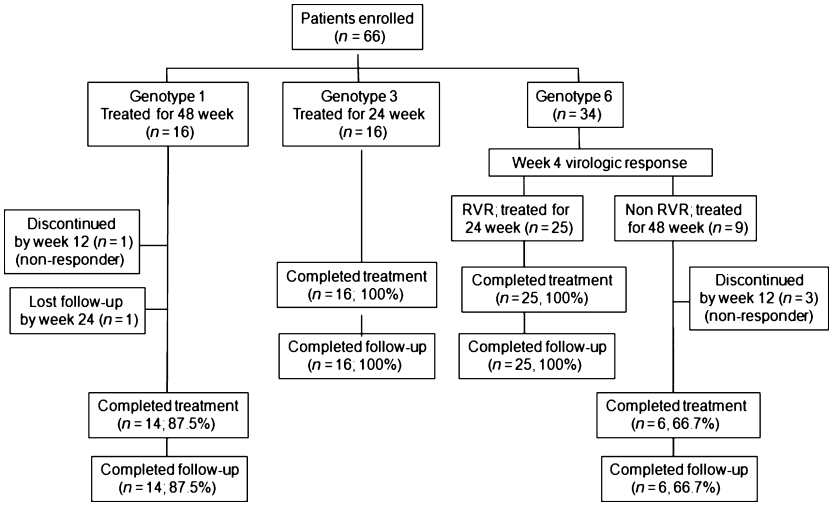

Fig. 1 Flow diagram of the patients enrolled in the study. RVR, rapid virological response (undetectable hepatitis C virus RNA at week 4).

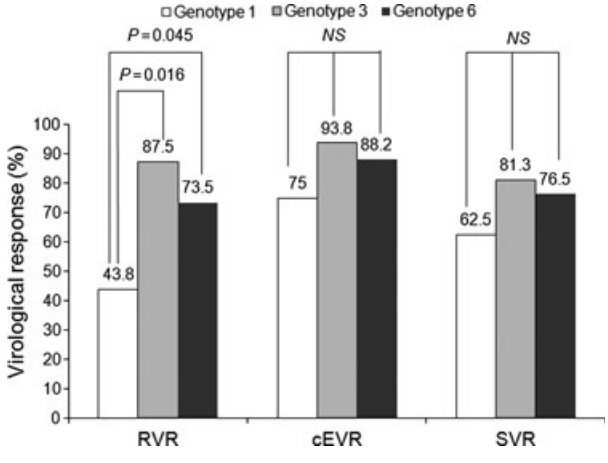

Fig. 2 Rates of virological response according to hepatitis C virus genotypes by intention-to-treat analysis. RVR, rapid virological response; cEVR, complete early virological response; SVR, sustained virological response; NS, no statistical significance.

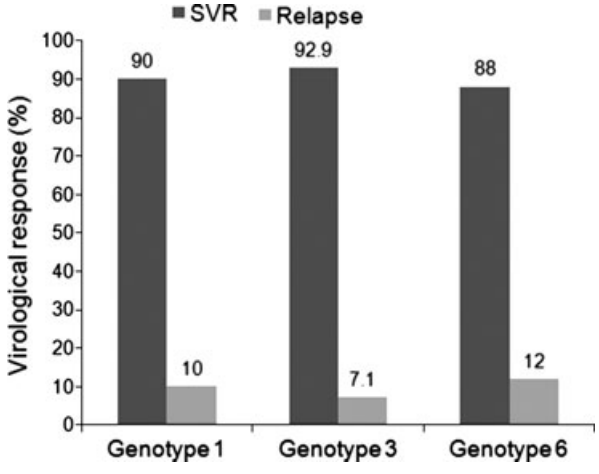

Fig. 3 Rates of sustained virological response (SVR) and relapse in patients achieving rapid virological response (RVR) according to hepatitis C virus genotypes.

($P = 0.704$) and was higher than in group 1 (10 of 16 patients; 62.5%), although there was no significant difference ($P = 0.245$ and $P = 0.309$, respectively).

Among patients who attained RVR, SVR was achieved in 9 of 10 (90%) patients in group 1, 13 of 14 (92.9%) patients in group 3 and 22 of 25 (88%) patients in RGT-group 6. The relapse rates among rapid responders in groups 1, 3 and RGT-group 6 were 10%, 7.1% and 12%, respectively. There was no statistical difference in terms of SVR and relapse rates among these groups (Fig. 3).

Among patients in RGT-group 6, the rates of cEVR and SVR were 100% and 88%, respectively. In this group, 10 of 10 (100%) patients with pretreatment viral load < 800 000 IU/mL and 12 of 15 (80%) patients with pretreatment viral load ≥ 800 000 IU/mL achieved SVR. For those in ST-group 6, the rates of cEVR and SVR were 55.5% and 44.4%, respectively, which were significantly lower than those in RGT-group 6 ($P = 0.035$ and $P = 0.025$, respectively) (Fig. 4). Patients in RGT-group 6 and ST-group 6 who achieved cEVR were likely to achieve SVR (88%, and 80%, respectively) Patients who did not achieve cEVR did not achieve SVR.

Predictors of SVR

To identify factors associated with SVR, baseline characteristics of patients and early viral kinetics during therapy were analysed by univariate and multivariate logistic regression

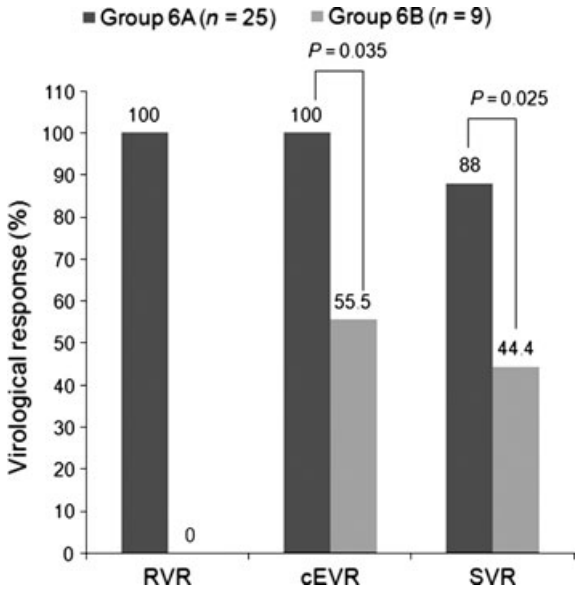

Fig. 4 Rates of virological response in groups 6A and 6B. RVR, rapid virological response; cEVR, complete early virological response; SVR, sustained virological response.

analyses. Potential predictors of SVR included sex, age, BMI, ALT level, liver fibrosis score, HCV genotype, HCV RNA level and achievement of RVR. A low HCV RNA level < 800 000 IU/mL (or $<\log_{10}$ 5.9 IU/mL) and achievement of RVR were factors predictive of SVR in univariate analysis. These factors were also independent predictors of SVR in multivariate analysis (Table 2).

Treatment adherence and safety assessment

Treatment adherence (defined as completion of at least 75–80% of intended dosage of PEG-IFN-α2a and at least 75–80% of intended dosage of RBV for at least 75–80% intended duration) was achieved in 81.3%, 75% and 82.5% of patients in group 1, 3 and 6, respectively (P = 0.825). A dose reduction of PEG-IFN-α2a was required in 12.5%, 18.8% and 14.7% of patients in group 1, 3 and 6, respectively (P = 0.881). A dose reduction of RBV was required in 25%, 31.3% and 26.5% of patients in group 1, 3 and 6, respectively (P = 0.914). None of the patients in this study discontinued the therapy because of serious adverse side effects.

DISCUSSION

Currently, the treatment outcome of patients with genotype 6 has not been adequately studied because of the limited number of cases in western countries. However, the optimal treatment duration of HCV genotype 6 is a particularly important consideration in south China and many southeast Asian countries in which this genotype is prevalent [18,19]. Most prior studies of HCV genotype 6 included patients treated for 48–52 weeks [12,20,21]. Recently, a small study of Asian American patients comparing a 48-week to a shortened 24-week regimen showed that a significantly higher SVR rate was achieved in those treated by the 48-week course (75% *vs* 49%) [22]. However, the limitation of the study was its retrospective design and the results were not analysed with regard to an intention-to-treat method. A retrospective study conducted in China showed that the rate of SVR in 22 patients with genotype 6 treated for 24 weeks was comparable with that of genotypes 2/3 (82% and 83%, respectively) [10]. In that study, the positive predictive values of RVR and EVR for HCV genotype 6 were comparable with those for genotypes 2/3 (87% *vs* 91% and 86% *vs* 87%, respectively). More recently, a randomized controlled trial of 60 patients with genotype 6 demonstrated that there was no significant difference in SVR rates in patients treated with 48-week and 24-week regimens (79% and 70%, respectively) [13]. In that study, RVR was a significant predictor of SVR in the 48-week group and tending towards significance in the 24-week group, although a sizeable number of patients did not have RVR measurement performed. These data indicate that 24 weeks of PEG-IFN plus RBV could effectively treat a subset of patients with genotype 6. However, the feasibility of a response-guided therapy by individualizing the duration of treatment according to viral kinetics in patients with genotype 6 has never been investigated.

To our knowledge, the present report is the first study directly examining the optimal duration of therapy based on RVR in patients with genotype 6. In this study, more than 70% of patients with genotype 6 achieved RVR and received an abbreviated 24-week regimen. Among these patients, the rate of relapse was approximately 10%, and nearly 90% of them eradicated the virus. These data are consistent with observations regarding treatment of HCV genotypes 1, 2, 3 and 4 [23],which suggest that monitoring RVR might be useful to guide treatment duration for patients with genotype 6. In particular, therapy might be shortened to 24 weeks in patients with genotype 6 achieving RVR, whereas a 48-week course was appropriate for those who cleared the virus after week 4. Thus, the integration of RVR into treatment decisions might identify patients with genotype 6 for whom an abbreviated course of therapy has proven to be satisfactory. The abbreviated regimen could offer advantages by reducing unnecessary medication exposure, which may make the treatment of HCV genotype 6 more affordable and maximize the cost effectiveness of therapy.

Several prospective trials of PEG-IFN and RBV have examined the use of RVR to select patients with HCV genotype 1 and non-1 genotypes for abbreviated therapy [15,24–26]. These studies have shown that a subset of patients with genotypes 2/3 and genotypes 1/4 who achieve RVR may be able to shorten therapy to 12–16 weeks, and 24 weeks, respectively, if certain pretreatment conditions are fulfilled. In recent meta-analyses of randomized

Table 2 Univariate and multivariate logistic regression analysis of pretreatment characteristics and on-treatment viral kinetics parameters to predict sustained virological response (SVR) in patients with genotype 6

			Univariate analysis	Multivariate analysis	
Factors	*N*	SVR (%)	*P*	Odd ratio (95% CI)	*P*
Age (year)					
<45	22	68.2	0.21	–	
≥45	12	91.7			
Sex					
Male	23	65.6	0.227	–	
Female	11	90.9			
BMI (kg/m^2)					
<25	25	80.0	0.649	–	
≥25	9	66.7			
ALT (U/L)					
<80	26	80.8	0.355	–	
≥80	8	62.5			
Liver fibrosis score					
Score 0–2	26	76.9	0.444	–	
Score 3–4	8	62.5			
Log HCV RNA (IU/mL)					
<5.9	12	100	0.030	2.40 (0.30–4.50)	0.029
≥5.9	22	63.6			
RVR					
RVR	25	88.0	0.017	4.51 (1.22–8.79)	0.013
Non-RVR	9	44.4			

ALT, alanine aminotransferase; BMI, body mass index; RVR, rapid virological response; cEVR, complete early virological response; CI, confidence interval.
Factors with a *P* value <0.05 by univariate analysis were entered in multivariate logistic regression analysis.

controlled trials, it has been demonstrated that abbreviated therapies do not significantly compromise the likelihood of SVR among rapid responders with most favourable characteristics for SVR, including genotype 1 or 2 with low viral load and genotype 3 with a weight-adjusted RBV regimen [27]. On multivariate analysis, the independent factors associated with SVR among patients with genotype 6 in this study were RVR and low pretreatment viral load. In fact, all rapid responders with low pretreatment viral load eventually eradicated HCV infection after completing 24 weeks of therapy, whereas the relapse rate was relatively high (20%) in rapid responders with high pretreatment viral load. These data suggested that abbreviated therapy for HCV genotype 6 might be particularly effective for rapid responders who had low pretreatment viral load. However, owing to the small sample sizes analysed, the ability to draw conclusions was rather limited, and further studies would be required before an abbreviated course could be generally recommended.

In this study, we found that the rate of RVR in patients with genotype 6 was slightly lower than that of genotype 3 (74% and 88%, respectively), but was significantly higher than that of genotype 1 (44%). These results might reflect a predictive indicator of the subsequent SVR rate of patients with genotype 6, which was at an intermediate level between those of genotypes 3 and 1, as demonstrated in previous reports [8–11]. It should be mentioned that patients with genotype 2 have higher SVR rates than patients with genotype 3 [28]. Thus, it is speculated that patients with genotype 2 should have a higher probability of achieving SVR than patients with genotype 6. Also of interest was the observation that, although the proportion of patients achieving RVR varied by genotype, the probability of achieving SVR was consistently high (88–93%) across all genotypes among patients who achieved RVR. This result is consistent with previous data that patients who achieve RVR have the highest rates of SVR (80–90%), regardless of HCV genotype [23].

Although PEG-IFN represents the backbone of treatment, combination with RBV has been shown to directly influence the outcome of therapy in that it prevents relapse. Current guidelines recommend a weight-adjusted dose of RBV in combination with PEG-IFN for treating patients with genotype 1, while a flat, low dose of RBV (800 mg/day) is recommended for treating patients with genotype 3 [7]. However, a weight-adjusted dose of RBV might be useful to enhance the response rate in patients with genotype 3 who

do not achieve RVR and in those with RVR undergoing abbreviated therapy [29,30]. Currently, the optimal dose of RBV for the treatment of patients with genotype 6 is unknown. In previous studies, daily weight-based or fixed doses of RBV had been used, rendering comparisons rather complicated. Nonetheless, a recent prospective trial has adopted a weight-based dosage of RBV for abbreviated treatment (24 weeks), which might result in achieving SVR equivalent to that obtained with longer treatment duration (48 weeks) [13]. In our study, all patients, regardless of HCV genotypes, received a weight-adjusted dose of RBV (1000–1200 mg/day). Taken together, these data might reflect the need of a weight-based dosage of RBV in patients with genotype 6 undergoing abbreviated therapy.

Regarding risk factors for HCV acquisition, our data showed that patients with genotype 6 had a significantly higher proportion of previous history of intravenous drug users compared with patients infected with other genotypes. This discrepancy might be due to the small sample size of the study because barely statistical significance was observed. In this respect, a recent larger study of Southeast Asian Americans did not find significant differences in terms of risk factors among patients with HCV genotypes 1, 2/3 and 6 [31]. In contrast, another study conducted in Hong Kong showed that patients with genotype 1 were mainly infected through blood transfusion, while a statistically larger proportion of patients with genotype 6 were infected through intravenous drug injection [11].

In conclusion, the results of this pilot study suggest that the overall response rate of HCV genotype 6 is slightly lower than that of genotype 3 but higher than that of genotype 1. Although the small sample size that might limit conclusions on utility of both RVR and EVR, our data suggest that a response-guided therapy based on viral kinetics may be useful to optimize treatment in patients with HCV genotype 6. In particular, shortened treatment duration of 24 weeks could be sufficient in patients with low pretreatment viral load who achieve RVR. Further prospective randomized trials are required to evaluate this response-guided strategy in a larger number of patients with genotype 6.

ACKNOWLEDGEMENTS

This study was supported by the National Research University Project of CHE and the Ratchadaphiseksomphot Endowment Fund (HR1162A), the Thailand Research Fund, and the Center of Excellence in Clinical Virology, Chulalongkorn University, Bangkok, Thailand. The study was also funded in part by Roche (Thailand). The authors would like to thank Ms P. Hirsch for editing the manuscript.

CONFLICT OF INTEREST STATEMENTS

The authors who have taken part in this study declare that they do not have anything to disclose regarding conflict of interest with respect to the manuscript.

REFERENCES

1 Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009; 29(Suppl. 1): 74–81.
2 Argentini C, Genovese D, Dettori S, Rapicetta M. HCV genetic variability: from quasispecies evolution to genotype classification. *Future Microbiol* 2009; 4(3): 359–373.
3 Fishman SL, Branch AD. The quasispecies nature and biological implications of the hepatitis C virus. *Infect Genet Evol* 2009; 9(6): 1158–1167.
4 Chao DT, Abe K, Nguyen MH. Systematic review: epidemiology of hepatitis C genotype 6 and its management. *Aliment Pharmacol Ther* 2011; 34(3): 286–296.
5 Akkarathamrongsin S, Praianantathavorn K, Hacharoen N *et al.* Geographic distribution of hepatitis C virus genotype 6 subtypes in Thailand. *J Med Virol* 2010; 82(2): 257–262.
6 Sunanchaikarn S, Theamboonlers A, Chongsrisawat V *et al.* Seroepidemiology and genotypes of hepatitis C virus in Thailand. *Asian Pac J Allergy Immunol* 2007; 25(2–3): 175–182.
7 Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology (Baltimore, MD)* 2009; 49(4): 1335–1374.
8 Nguyen NH, VuTien P, Garcia RT *et al.* Response to pegylated interferon and ribavirin in Asian American patients with chronic hepatitis C genotypes 1 vs 2/3 vs 6. *J Viral Hepat* 2010; 17(10): 691–697.
9 Tsang OT, Zee JS, Chan JM *et al.* Chronic hepatitis C genotype 6 responds better to pegylated interferon and ribavirin combination therapy than genotype 1. *J Gastroenterol Hepatol* 2010; 25(4): 766–771.
10 Zhou YQ, Wang XH, Hong GH *et al.* Twenty-four weeks of pegylated interferon plus ribavirin effectively treat patients with HCV genotype 6a. *J Viral Hepat* 2011; 18(8): 595–600.
11 Seto WK, Lai CL, Fung J *et al.* Natural history of chronic hepatitis C: genotype 1 versus genotype 6. *J Hepatol* 2010; 53(3): 444–448.
12 Fung J, Lai CL, Hung I *et al.* Chronic hepatitis C virus genotype 6 infection: response to pegylated interferon and ribavirin. *J Infect Dis* 2008; 198(6): 808–812.
13 Lam KD, Trinh HN, Do ST *et al.* Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. *Hepatology (Baltimore, MD)* 2010; 52(5): 1573–1580.
14 de Leuw P, Sarrazin C, Zeuzem S. How to use virological tools for the optimal management of chronic hepatitis C. *Liver Int* 2011; 31(Suppl. 1): 3–12.
15 Ferenci P, Laferl H, Scherzer TM *et al.* Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology* 2008; 135(2): 451–458.

16 Jensen DM, Morgan TR, Marcellin P *et al.* Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology (Baltimore, MD)* 2006; 43(5): 954–960.
17 Zeuzem S, Buti M, Ferenci P *et al.* Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 2006; 44(1): 97–103.
18 Antaki N, Marcellin P. What is the safe duration of therapy for patients infected with HCV genotype 6? *Nat Clin Pract* 2009; 6(2): 78–79.
19 Antaki N, Craxi A, Kamal S *et al.* The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver Int* 2010; 30(3): 342–355.
20 Hui CK, Yuen MF, Sablon E, Chan AO, Wong BC, Lai CL. Interferon and ribavirin therapy for chronic hepatitis C virus genotype 6: a comparison with genotype 1. *J Infect Dis* 2003; 187(7): 1071–1074.
21 Dev AT, McCaw R, Sundararajan V, Bowden S, Sievert W. Southeast Asian patients with chronic hepatitis C: the impact of novel genotypes and race on treatment outcome. *Hepatology (Baltimore, MD)* 2002; 36(5): 1259–1265.
22 Nguyen MH, Trinh HN, Garcia R, Nguyen G, Lam KD, Keeffe EB. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. *Am J Gastroenterol* 2008; 103(5): 1131–1135.
23 Fried MW, Hadziyannis SJ, Shiffman ML, Messinger D, Zeuzem S. Rapid virological response is the most important predictor of sustained virological response across genotypes in patients with chronic hepatitis C virus infection. *J Hepatol* 2011; 55(1): 69–75.
24 Dalgard O, Bjoro K, Ring-Larsen H *et al.* Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology (Baltimore, MD)* 2008; 47(1): 35–42.
25 Mangia A, Bandiera F, Montalto G *et al.* Individualized treatment with combination of Peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3. *J Hepatol* 2010; 53(6): 1000–1005.
26 Yu ML, Dai CY, Huang JF *et al.* Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology (Baltimore, MD)* 2008; 47(6): 1884–1893.
27 Di Martino V, Richou C, Cervoni JP *et al.* Response-guided Peg-interferon plus ribavirin treatment duration in chronic hepatitis C: meta-analyses of randomized controlled trials and implications for the future. *Hepatology (Baltimore, MD)* 2011; 54(3): 789–800.
28 Shiffman ML, Suter F, Bacon BR *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; 357(2): 124–134.
29 Mangia A. Individualizing treatment duration in hepatitis C virus genotype 2/3-infected patients. *Liver Int* 2011; 31(1): 36–41.
30 Martin P, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 2008; 23(6): 844–855.
31 Nguyen NH, Vutien P, Trinh HN *et al.* Risk factors, genotype 6 prevalence, and clinical characteristics of chronic hepatitis C in Southeast Asian Americans. *Hep Intl* 2010; 4(2): 523–529.