Meta-Analysis: Superior Treatment Response in Asian Patients with Hepatitis C Virus Genotype 6 versus Genotype 1 with Pegylated Interferon and Ribavirin

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Key Words

Hepatitis C virus · Sustained virologic response · Genotype 6 · Genotype 1

Abstract

Objective: Our goal was to systematically and quantitatively assess treatment response between Asian patients with hepatitis C virus genotype 6 (HCV-6) and hepatitis C virus genotype 1 (HCV-1) treated for 48 weeks with pegylated interferon and ribavirin. **Methods:** We performed a literature search in MEDLINE and EMBASE for ‘genotype 6’ in August 2013. Additional abstracts from major international scientific conferences from 2012 to 2013 were reviewed. Studies included were original articles with ≥ 10 treatment-naïve Asian HCV-6 patients. Exclusion criteria were coinfections with hepatitis B virus, HIV and/or other liver diseases. Heterogeneity was defined as a Cochrane Q test with a p value of 0.10 and an I^2 statistic of $>50\%$. Results of a random-effects model are reported. **Results:** A total of 1,046 (503 HCV-6; 543 HCV-1) patients from 12 studies were included in the analysis. The pooled sustained virologic response (SVR) rate was

80.2% (95% CI 74.3–85.0, Q statistic = 20.87, $p < 0.035$; $I^2 = 47.3\%$) for HCV-6 and 62.5% (95% CI 41.9–79.4, Q statistic = 52.41, $p < 0.001$; $I^2 = 92.37\%$) for HCV-1 patients. HCV-6 patients had a significantly higher SVR rate compared to HCV-1 patients (odds ratio 2.73, 95% CI 1.69–4.41, $p < 0.001$). Approximately one fourth of patients without early virologic response (EVR) achieved SVR, regardless of genotype (HCV-1, $n = 6/23$; HCV-6, $n = 4/21$). **Conclusions:** Asian patients with HCV-6 can expect higher SVR rates (~80%) than HCV-1 patients (~63%). EVR as a stopping rule is less clear in Asian patients with HCV-6 and HCV-1.

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Introduction

Chronic infection with hepatitis C virus (HCV) is a major global health problem affecting approximately 170 million people [1]. Chronic infection causes significant sequelae and frequently leads to end-stage liver disease and hepatocellular carcinoma [2]. In Southeast Asia, HCV prevalence in some countries (6–7% in Vietnam

and Thailand) is higher than the US prevalence of 1.8% [1]. HCV genotype 1 (HCV-1) and the lesser known genotype 6 (HCV-6) are also the 2 most common genotypes in parts of Southeast Asia, Hong Kong and Southern China [1].

HCV genotype is a major independent predictor of sustained virologic response (SVR, defined as undetectable HCV RNA at 24 weeks after the end of therapy) in patients treated with pegylated interferon and ribavirin (PEG-IFN + RBV) [1]. While there are 6 known HCV genotypes worldwide, HCV genotypes 1–3 are predominant in Western countries, and large registration trials with PEG-IFN + RBV have been conducted and focused on these 3 genotypes. HCV-1 (40–50%) has lower SVR rates than the more treatment-favorable genotypes 2 and 3 (70–80%) [2]. However, results from these studies often stem from non-Asian patients and may not be generalizable to Asian patients.

Although there have been several studies published on Asian patients with HCV-1, there is limited treatment information on Asian patients with HCV-6 and even less data directly comparing SVR rates in patients with these 2 genotypes [3–12]. Some studies suggest that the SVR rate in HCV-6 patients is superior to that in HCV-1 patients, but these studies are largely limited by their small sample sizes [4, 10–21].

Most recently, triple therapy with PEG-IFN + RBV and sofosbuvir has been approved by the Food and Drug Administration in the US for the treatment of HCV-1 [22]. However, given the high retail cost of sofosbuvir (Sovaldi[®], Gilead Sciences, Foster City, Calif., USA; USD 84,000 for 12 weeks of treatment in the USA), this therapy may be cost prohibitive [22, 23]. While Gilead Sciences has proposed price reductions for low- to middle-income countries (USD 5,000 in Thailand, USD 2,000 in India), comments from directors of the Médecins sans Frontières Access Campaign [24] suggest that ‘at these prices, access in middle-income countries – where 75% of the world’s poor actually live – is likely to be extremely limited’, given the income disparity in such areas. Data on new direct-acting antiviral therapy for HCV-6 is also very limited with only 6 patients with HCV-6 included in the landmark NEUTRINO study with sofosbuvir-based therapy [25]. Therefore, PEG-IFN + RBV will likely remain the main therapeutic option for Asian patients residing in these regions for the near future.

Our goal was to quantitatively and qualitatively compare treatment responses to PEG-IFN + RBV between Asian patients infected with HCV-6 versus HCV-1.

Materials and Methods

Data Sources and Searches

We performed a comprehensive literature search in PubMed in October 2013 with the search term ‘genotype 6’. The search was limited to MEDLINE-indexed articles only and included studies in non-English languages. We also performed a manual search for the term ‘genotype 6’ in abstracts from annual international scientific meetings between 2012 and 2013 of the American Association for the Study of Liver Diseases (AASLD), Digestive Disease Week (DDW), Asian Pacific Study of the Liver (APASL) and European Association for the Study of the Liver (EASL). An EMBASE search was also conducted for the same period using the search term ‘genotype 6/exp’.

Study Selection

Original studies with ≥ 10 HCV-6 treatment-naïve Asian patients treated with PEG-IFN + RBV were included. Studies were excluded if study cohorts included patients with coinfection with hepatitis B, hepatitis D or HIV. In studies that included both HCV-6 and HCV-1 patients, we included these HCV-1 patients as the HCV-1 comparison group for our study. Articles were reviewed independently by two of the authors (N.H.N. and S.A.M.) and checked by a third author (M.H.N.), discrepancies being resolved by consensus.

Data Extraction

For each study, we collected information on study characteristics (country of origin, practice setting, collaboration), study design, study type [randomized controlled trial (RCT) vs. observational], intention-to-treat (ITT) analysis and baseline patient characteristics (ethnicity, age, gender, alanine transferase, fibrosis and HCV RNA levels). We also collected baseline treatment information and treatment response data, namely rapid virologic response (RVR, defined as undetectable HCV RNA after 4 weeks of treatment), early virologic response (EVR, defined as <50 IU/ml or >2 -log drop from baseline HCV RNA after 12 weeks of treatment) and SVR.

Statistical Analysis

Pooled event rates and odds ratios (ORs) with corresponding 95% CIs were gathered using random-effects models and the inverse variance method [26]. Study heterogeneity was assessed through a χ^2 -based Cochrane Q statistic, with $p \leq 0.10$ and $I^2 \geq 50\%$ considered substantial heterogeneity [26]. Influence analysis to ensure the robustness of the pooled estimate was conducted for the primary outcome. In studies with zero cell counts, a fixed value of 0.5 was added to all cells of the study result tables [26]. All statistical tests were 2-sided. All calculations were performed using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, N.J., USA).

Results

Study Search Results

In total, we identified 161 and 251 articles through PubMed and EMBASE, respectively, and 14,648 abstracts

Fig. 1. Flowchart of studies included.

from AASLD, DDW, APASL and EASL. Forty-one studies were identified and assessed for more detailed evaluation and inclusion for analysis [4, 10–12, 14–21, 27–53]. Ten studies did not contain original or extractable data for analysis [13, 45–53]. Eight studies were identified as redundant and thus excluded; these were duplicates found during our search or earlier abstracts of full articles that were later published [15, 19, 28–31, 40, 41]. Six studies included less than 10 HCV-6 patients [32–34, 42–44]. Four studies did not include patients treated with PEG-IFN + RBV [35–38]. One study included patients with coinfections [41]. Ultimately, 12 studies (8 full articles and 4 abstracts) [4, 10–12, 14–21] met our inclusion criteria and were included in this meta-analysis (fig. 1). All 12 studies included HCV-6 patients treated for 48 weeks. The characteristics of the 12 studies are described in table 1.

Study and Patient Characteristics

In the primary analysis, a total of 1,046 (503 HCV-6; 543 HCV-1) patients from 12 studies were included (table 1).

Six studies were prospective, 4 were retrospective and 2 were of unknown design [4, 10–12, 14–21]. Of the 12 studies, 2 were RCTs [20, 21], while the remaining studies were observational or nonrandomized trials [4, 10–12, 14–19]. Study origins included 3 from the USA [14, 15, 21], 3 from Southeast Asia (1 from Thailand and 2 from Vietnam) [11, 16, 20] and 6 from China [4, 10, 12, 16–18]. The majority of studies were performed in a university or tertiary referral setting. All studies evaluated SVR overall and in Asian patients with HCV-6 [4, 10–12, 14–21]. Five studies directly compared Asian patients with HCV-6 versus HCV-1 [4, 10–12, 15]. All subjects were Asian and most of them were male. Only patients treated with PEG-IFN + RBV for 48 weeks were included in the analysis.

SVR in HCV-6 and HCV-1 Patients Treated for 48 Weeks

The pooled event rate of SVR in 503 HCV-6 patients was 80.2% (95% CI 74.3–85.0, Q statistic = 20.87, $p < 0.035$; $I^2 = 47.3\%$) [4, 10–12, 14–21]. In a funnel plot anal-

Table 1. Characteristics of studies included in the treatment analysis of Asian patients with HCV-6 and HCV-1

Study	Population	HCV-6			HCV-1		
		males, n	age, years	n	males, n	age, years	n
Tangkijvanich et al. [11], 2012	Thailand	23 (68)	41.2±8.4	34	9 (56)	46.4±12.5	16
Thu Thuy et al. [20], 2012	Vietnam	65 (62)	48.6±8.4	70	n.a.	n.a.	n.a.
Lam et al. [21], 2010	USA	28 (47)	52.8±8.0	33	n.a.	n.a.	n.a.
Tsang et al. [12], 2010	Hong Kong	47 (67)	50	70	44 (63)	48	70
Nguyen et al. [60], 2012	USA	34 (56)	49.4±10.8	34	51 (73)	50±9.7	70
Fung et al. [4], 2008	Hong Kong	11 (52)	49.5 (14–64)	21	12 (57)	52 (30–63)	21
Nguyen et al. [14], 2008	USA	45 (68)	50±10	12 ^a	n.a.	n.a.	n.a.
Seto et al. [18], 2013	Hong Kong	41 (68)	49	60	n.a.	n.a.	n.a.
Shao et al. [19], 2012	China	unknown	unknown	28	n.a.	n.a.	n.a.
Cai et al. [17], 2011	China	unknown	unknown	84	n.a.	n.a.	n.a.
Pham et al. [16], 2009	Vietnam	unknown	unknown	42	n.a.	n.a.	n.a.
Rao et al. [10], 2013	China	unknown	unknown	14	unknown	unknown	365

Results are reported as means ± SD, numbers with percentages given in parentheses or medians of study populations with ranges given in parentheses and do not necessarily reflect only patients with HCV-6 and HCV-1. n.a. = No data available.

^a Thirty-one patients were treated with standard IFN therapy and were not included in the analysis.

ysis for publication bias, the study by Rao et al. [10] had the largest standard error, namely 1.5 (data not shown). This observation could be explained by the small sample of HCV-6 patients (n = 14) who achieved a 100% SVR success rate in their study. In an influence analysis using the 1-study removal method, there was only a small change (~1%) in the pooled event rate when their study was omitted, demonstrating the robustness of our estimate.

In the 9 studies with ITT analysis, the pooled event rate was 80.4% (95% CI 73.2–86.1), which was similar to the SVR rate observed in the 3 studies with non-ITT analysis (80.2%, 95% CI 66.3–89.2). Significant heterogeneity was not indicated in the subgroup study with ITT analysis (Q statistic = 13.03, p = 0.11; I² = 38.624). The SVR rate was lower in RCTs, 74.6% (95% CI 58.7–85.8), than in observational and nonrandomized studies, 81.6% (95% CI 75.2–86.7). We observed significant heterogeneity in the subgroup analysis with non-RCTs (Q statistic = 18.08, p = 0.034; I² = 50.208).

In the 5 studies with a total of 543 Asian HCV-1 patients, the pooled SVR rate was 62.5% (95% CI 41.9–79.4, Q statistic = 52.41, p < 0.001; I² = 92.37). All studies were observational in nature and analyzed SVR rates according to the ITT [4, 10–12, 15].

Direct Comparison between SVR Rates in Asian Patients with HCV-6 and HCV-1

In the 5 studies with a direct comparison between Asian patients with HCV-6 and HCV-1, there were a to-

tal of 174 HCV-6 and 543 HCV-1 patients. The pooled SVR rates were 77.1% (95% CI 70.0–82.9) and 62.5% (95% CI 41.9–79.4), respectively. There was a statistically significant difference between SVR rates in HCV-6 versus HCV-1 patients (OR 2.73, 95% CI 1.69–4.41, p < 0.001; fig. 2). These studies were all observational or nonrandomized in nature and analyzed SVR rates according to the ITT [4, 10–12, 15]. No significant heterogeneity was indicated (Q statistic = 1.56, p = 0.82; I² = 0%). Since I² was 0%, effect sizes and corresponding CIs were the same between both random- and fixed-effects models.

Rates of SVR in HCV-6 and HCV-1 Patients with EVR

In the 4 studies with EVR and SVR data of HCV-6 patients, there were a total of 207 HCV-6 patients [11, 12, 20, 21]. The pooled SVR rate overall in these studies was 74.8% (95% CI 68.4–80.2), while the pooled EVR rate was 88% (95% CI 82.6–91.9). In cases with EVR, 81.5% (95% CI 75.2–86.5) achieved SVR. Of the 21 patients who did not have an EVR, 23.8% (95% CI 7.0–56.5) subsequently achieved SVR. In the 3 studies with a direct comparison between HCV-6 patients with and without EVR, patients with EVR were significantly more likely to have SVR compared to those without EVR (OR 13.7, 95% CI 3.83–49.2, p < 0.001).

In the 2 studies that contained EVR data of HCV-1 patients, there were a total of 91 HCV-1 patients [4, 12].

Fig. 2. Comparison between patients with HCV-6 and HCV-1.

The pooled SVR rate in these studies was 56.0% (95% CI 45.7–65.9), while the pooled EVR rate was 74.7% (95% CI 64.8–82.6). In cases with EVR, 66.1% (95% CI 54.2–76.4) achieved an SVR [4, 12]. Of the 23 patients without EVR, 26.2% (95% CI 12.3–47.5) subsequently achieved SVR. Patients with EVR had a significantly higher OR of achieving SVR compared to patients without EVR (OR 5.59, 95% CI 1.93–16.2, $p = 0.002$).

Discussion

In the current meta-analysis, we included a total of 12 studies with 503 HCV-6 and 543 HCV-1 patients. The pooled SVR rate was 80.2% (95% CI 74.3–85.0) in HCV-6 patients and 62.5% (95% CI 41.9–79.4) in HCV-1 patients. HCV-6 patients were significantly more likely to achieve SVR compared to HCV-1 patients (OR 2.73, 95% CI 1.69–4.41, $p < 0.001$). Our result represents the first large and comprehensive study to date to evaluate SVR rates between these patients.

In cases with HCV-1, our pooled SVR rate (~60%) is higher than findings in non-Asian HCV-1 patients from large registration trials (~40–50%) and comparable to studies that specifically evaluated treatment data in Asian HCV-1 patients [3, 5–9]. The high SVR rates in our Asian patients with HCV-1 could be explained by the CC genotype (a polymorphism near interleukin-28 on chromo-

some 19 that influences SVR rates with IFN-based therapies) known to be more common in areas where most of these Asian patients with HCV-6 and HCV-1 reside [17, 18, 54, 55].

In our study, HCV-1 and HCV-6 patients with EVR were more likely to achieve SVR compared to those without EVR, which is consistent with the established literature on the positive predictive value of EVR [56]. However, approximately one fourth of patients without EVR also achieved SVR subsequently, regardless of genotypes. While previous studies have recommended that the absence of EVR is a good stopping rule in patients with HCV-1, data from this recommendation was derived from studies with largely non-Asian patients and/or small numbers of patients without EVR [2, 9, 56]. Two large RCTs with treatment-naïve Asian patients with HCV-1 by Liu et al. [9] ($n = 308$) and Yu et al. [57] ($n = 200$) also found that 0% of patients without EVR achieved SVR and also suggested that treatment could be stopped in those without EVR; their recommendations were based on data of a very small number of patients without EVR ($n = 4$ and $n = 7$, respectively). On the other hand, based on our meta-analysis data of the 23 HCV-1 patients without EVR, we cannot recommend stopping treatment in such patients without EVR, since a quarter of these patients eventually achieved SVR.

Additionally, the economic burden of not achieving SVR and/or retreatment is much higher in patients that do

not achieve SVR versus those that achieve SVR [58]. In this study by Backx et al. [58], the authors demonstrated that failure to achieve SVR was associated with a 13-fold increase in health care-related costs, which was related to a higher likelihood of a patient transitioning to a severer disease state that required more health care, while the costs were 56-fold higher for retreated patients. Given that PEG-IFN + RBV is associated with significant side effects and requires a full year of treatment, the risk, benefits and cost savings of treatment should be discussed with the patient, and the decision to continue treatment if a patient does not achieve EVR should be individualized.

While our data did not allow us to examine response-guided therapy for shortened treatment duration, data from 2 RCTs by Liu et al. [9] and Yu et al. [57] suggest that HCV-1 patients with RVR may be treated for 24 weeks with PEG-IFN + RBV. In contrast, for patients who continue to experience detectable HCV RNA after 24 weeks with PEG-IFN + RBV, studies have suggested that these patients may also stop treatment [2]. In Asian patients with HCV-6, an ongoing RCT with PEG-IFN + RBV in patients with RVR has produced results that suggest there are no significant differences between 24 and 48 weeks of treatment [59]. Until published data becomes available from this trial, patients with HCV-6 should be treated for 48 weeks with PEG-IFN + RBV.

One of the limitations of our meta-analysis was the small number of studies available, which affected our ability to detect significant publication bias and perform additional subgroup analyses. To account for the limited data available, we sought to be as inclusive as possible and included studies of relatively different characteristics. We also reported results from random-effects models in an at-

tempt to provide a more conservative estimate. Another limitation is the potential selection bias of patients, as most of our data were derived from observational studies. However, our findings are more likely to be generalizable to patients in routine clinical settings, since observational studies have broader inclusion criteria for study patients and are more likely representative of the population at large.

In summary, Asian patients with HCV-6 can expect a higher SVR rate (~80%) than Asian patients with HCV-1 when treated for 48 weeks with PEG-IFN + RBV (~63%). Lack of EVR may not be a good stopping rule for Asian patients with HCV-6 or HCV-1. Compared to the high cost of newer therapies, PEG-IFN + RBV may remain an acceptable option for Asian patients residing in resource-limited regions with HCV-6 and perhaps also for Asian patients with HCV-1, especially given the higher SVR rates with both genotypes with PEG-IFN + RBV in this ethnic group.

Acknowledgment

This study was funded in part by the NIH National Center for Research Resources, TL1 training grants and 1TL1RR03197, to Nghia H. Nguyen and Shelley A. McCormack.

Disclosure Statement

Nghia H. Nguyen, Shelley A. McCormack, Philip Vutien, Brittany E. Yee, Pardha Devaki and David Jencks have no conflicts of interest to declare.

Mindie H. Nguyen has served as a consultant and an advisory board member for Gilead Sciences Inc., Bristol-Myers Squibb, Novartis and Bayer.

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