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Meta-analysis: Superior treatment response in Asian patients with HCV genotype 6 versus 1 with pegylated interferon and ribavirin

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Abstract

Objective(s)—Our goal is to systematically and quantitatively assess treatment response between Asian patients with HCV-6 and HCV-1 treated for 48 weeks with PEG IFN+RBV.

Methods—We performed a literature search in Medline and EMBASE for ‘genotype 6’ in August 2013. Additional abstracts from major international scientific conferences from 2012–2013 were reviewed. Included studies were original articles with ≥10 treatment-naïve Asian HCV-6 patients. Exclusion criteria were co-infections with HBV, HIV and/or other liver diseases. Heterogeneity was defined as Cochrane Q-test with *p*-value of 0.10 and I-squared statistic (>50%). Results are reported from random-effects model.

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Conflict of Interest

Nghia H. Nguyen, Shelley A. McCormack, Philip Vutien, Brittany E. Yee, Pardha Devaki, David Jencks: None declared.
Mindie H. Nguyen has served as a consultant and an advisory board member for Gilead Sciences Inc, Bristol-Myers Squibb, Novartis, and Bayer.

Author’s contributions

Guarantor of article: Dr. Mindie Nguyen
Nghia Nguyen: study design, acquisition of data, data analysis, statistical analysis, and interpretation and drafting of the manuscript, obtained funding
Shelley McCormack: acquisition of data, data interpretation, and critical review of the manuscript, obtained funding
Philip Vutien: data collection and critical review of the manuscript.
Brittany Yee: data analysis and critical review of the manuscript.
Pardha Devaki: study design and critical review of the manuscript.
David Jencks: study design and critical review of the manuscript.
Mindie Nguyen: concept development, study design, data collection, data analysis and interpretation, and critical revision of the manuscript.
All authors identified above have critically reviewed the paper and approve the final version of this paper, including the authorship statement.

Results—A total of 1046 (503 HCV-6; 543 HCV-1) patients from 12 studies were included in the analysis. Pooled SVR rate was 80.2% (CI 74.3–85.0%) (Q-statistic=20.87, p<0.035; I2=47.3%) for HCV-6 and 62.5% (CI 41.9–79.4%) (Q-statistic=52.41, p<0.001; I2=92.37) for HCV-1 patients, respectively. HCV-6 patients had significantly higher SVR rate compared to HCV-1 patients, OR 2.73 (CI 1.69–4.41, *p*<0.001). Approximately one-fourth of patients without EVR achieved SVR, regardless of genotype (n = 6/23 HCV-1; n = 4/21 HCV-6).

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.

Keywords

HCV; hepatitis C; sustained virologic response; genotype 6; genotype 1

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is a major global health problem infecting 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 U.S. prevalence of 1.8%[1]. HCV genotype 1 (HCV-1) and the lesser known genotype 6 (HCV-6) are also the two 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 end of therapy) in patients treated with pegylated interferon and ribavirin (PEG IFN+RBV) [1]. While there are six 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 genotypes. HCV genotype 1 (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 are often in 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 two genotypes [3–12]. Some studies suggest that SVR rate in HCV-6 patients is superior to HCV-1, but they 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 U.S. for the treatment of HCV-1 [22]. However, given the high retail cost of sofosbuvir (Sovaldi®, Gilead Sciences, Foster City, CA, USA) ($84,000 for 12 weeks of treatment in the U.S.), this therapy may be cost-prohibitive [22,23]. While Gilead Sciences has proposed price reductions for low- to middle-income countries ($5,000 in Thailand, $2,000 in India), comments from directors from Médecins Sans Frontières' Access Campaign 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

[24],” given the income disparity in such areas. Data on new direct acting antiviral therapy for HCV genotype 6 is also very limited with only 6 patients with HCV genotype 6 included in the landmark NEUTRINO study with sofosbuvir-based therapy [25]. Therefore, PEG-IFN + RBV will likely remain the main therapeutic option in Asian patients residing in these regions for the near future.

Our goals are to quantitatively and qualitatively compare treatment responses to PEG-IFN and 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 following 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 of abstracts using the term ‘genotype 6’ from annual international scientific meetings between 2012 and 2013 by 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 search criteria: (‘genotype 6’/exp).

Study Selection

Studies fulfilling the following specific inclusion criteria were considered for analysis: i) original studies ii) inclusion of treatment-naïve Asian patients iii) minimum sample size of ≥10 HCV-6 patients iv) inclusion of patients treated with PEG IFN+RBV. Studies were excluded if study cohorts included patients with co-infection with hepatitis B, hepatitis D, or human immunodeficiency virus. 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. Nguyen and S. McCormack) and checked by a third author (M. Nguyen) with discrepancies 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 (RCTs) versus observational), intention-to-treat (ITT) analysis, and baseline patient characteristics (ethnicity, age, gender, ALT, fibrosis, and HCV RNA levels). We also collected baseline treatment information and treatment response (rapid virologic response [RVR, defined as undetectable HCV RNA after 4 weeks of treatment], early virological response [EVR, defined as <50 IU/mL or >2 log drop from baseline HCV RNA after 12 weeks of treatment] and SVR).

Statistical Analysis

Statistical analyzes were performed to produce pooled event rates (SVR rates in HCV-6 and HCV-1 patients treated for 48 weeks) with corresponding 95% confidence intervals using random-effects models and inverse variance method [26]. Odds ratios (OR) and

corresponding 95% confidence intervals were produced for subgroup analyzes. Study heterogeneity was assessed through χ^2-based Cochrane Q-statistic with $p \leq 0.10$ and $I^2 \geq 50\%$ considered substantial heterogeneity [26]. Influence analysis to ensure robustness of pooled estimate was conducted for the primary outcome. We also assessed for potential publication bias graphically with a funnel plot of ln[OR] against its standard error (SE) where appropriate. In studies with zero-cell counts, a fixed value of '0.5' was added to all cells of study results tables [26]. All statistical tests were two-sided. All calculations were performed using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey, USA).

RESULTS

Study Search Results

In total, we identified 161 and 251 articles through PubMed and EMBASE, respectively, and 14,648 abstracts from AASLD, DDW, APASL, and EASL. Forty-one studies were identified and assessed for more detailed evaluation and inclusion for analysis [4,10–12,14–20,27–56]. Ten studies did not contain original or extractable data for analysis [13,48–56]. Eight studies were identified as redundant and excluded: duplicates found during our search or earlier abstracts of full articles that were later published [15,19,30–33,42,43]. Six studies included less than ten HCV-6 patients [34–36,44–46]. Four studies did not include patients treated with PEG IFN+RBV [37–40]. One study included patients with co-infections [41]. Ultimately, twelve (eight full articles and four abstracts) met inclusion criteria and were included in this meta-analysis (Figure 1)[4,10–12,14–21]. All twelve studies included HCV-6 patients treated for 48 weeks [4,10–12,14–21]. Characteristics of the twelve studies are described in Table 1.

Study and Patient Characteristics

In the primary analysis, a total of 1046 (503 HCV-6; 543 HCV-1) patients from 12 studies were included (Table 1). Six studies were prospective, four were retrospective and two were unknown [4,10–12,14–21]. Of the twelve studies, two were RCTs [20,21], while the remaining studies were observational or nonrandomized trials [4,10–12,14–19]. Study origins included three from North America (USA) [14,15,27], three from Southeast Asia (one in Thailand and two from Vietnam) [11,16,20], and six from China [4,10,12,16–18]. The majority of studies occurred 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 mostly 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

Pooled event rate of SVR in 503 HCV-6 patients was 80.2% (95% CI 74.3–85.0%)(Q-statistic=20.87, $p<0.035$; $I^2=47.3\%$) (Figure 2). On funnel plot analysis for publication bias, the study by Rao H *et al* had the largest standard error, 1.5 (data not shown). This observation could be explained by the small sample of HCV-6 patients (n=14) who achieved 100% success rate of SVR in this study [10]. On influence analysis with one-study removal

method, there was only a small change (~1%) in the pooled event rate when this study was omitted demonstrating the robustness of our estimate.

In the nine 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 three studies with non-ITT 80.2% (95% CI 66.3–89.2%). Significant heterogeneity was not indicated in the sub-group analysis with ITT study (Q-statistic = 13.03, p=0.11; I^2=38.624). SVR rate was lower in RCTs, 74.6% (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; I^2=50.208).

In the five studies with a total of 543 Asian HCV-1 patients, pooled SVR rate was 62.5% (95% CI 41.9–79.4%) (Q-statistic=52.41, p<0.001; I^2=92.37). All studies were observational in nature and analyzed SVR rates according to ITT [4,10–12,15].

Direct comparison between SVR rates in Asian patients with HCV-6 and HCV-1

In the five studies with direct comparison between Asian patients with HCV-6 and HCV-1, there were a total of 174 HCV-6 and 543 HCV-1 patients. 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). These studies were all observational or nonrandomized in nature and analyzed SVR rates according to ITT [4,10–12,15]. No significant heterogeneity was indicated (Q-statistics=1.56, p=0.82; I2=0%). Since I^2 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 four studies with EVR and SVR data in HCV-6 patients, there were a total of 207 HCV-6 patients [11,12,20,21]. Pooled SVR rate overall in these studies was 74.8% (95% CI 68.4–80.2%), while pooled EVR rate was 88% (95% CI 82.6–91.9%). In patients with EVR, 81.5% (95% CI 75.2–86.5%) achieved SVR. Of the 21 patients who did not have EVR, 23.8% (95% CI 7.0–56.5%) subsequently achieved SVR. In the three studies with 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 two studies that contained EVR data in HCV-1 patients, there were a total of 91 HCV-1 patients [4,12]. Pooled SVR rate in these studies was 56.0% (95% CI 45.7–65.9%), while pooled EVR rate was 74.7% (95% CI 64.8–82.6%). In patients with EVR, 66.1% (95% CI 54.2–76.4%) achieved 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 odds 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 patients and 543 HCV-1. 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 patients 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 rates of SVR in our Asian patients with HCV-1 could be explained by multiple factors: specific host factors, genetic markers and more-treatment favorable polymorphism (CC genotype) near the gene IL-28 on chromosome 19 that influences SVR rates in patients treated with interferon-based therapies [57,58]. The CC genotype is known to be more common in areas where most of these Asian patients with HCV-6 and HCV-1 reside [17,18,57,58].

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 [59]. However, approximately one-fourth of patients without EVR also subsequently achieved SVR, 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 [2,9,59]. Two large RCTs in treatment-naïve Asian patients with HCV-1 by Liu CH *et al* (n = 308) and Yu ML *et al* (n = 200) also found that 0% of patients without EVR achieved SVR and also suggested that treatment can 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)[9,60]. On the other hand, based on data from 23 HCV-1 patients without EVR from this meta-analysis, we cannot recommend stopping treatment in those without the presence of 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 [61]. In a study by Backx *et al*, the authors demonstrated that failure to achieve SVR was associated with a 13-fold increase in healthcare-related costs, which was related to a higher likelihood of a patient transitioning to a more severe disease state that required more healthcare, while the costs were 56-fold higher for retreated patients [61]. 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 two RCTs by Liu CH *et al* and Yu ML *et al*, suggest that HCV-1 patients with RVR may be treated for 24 weeks with PEG-IFN+RBV [9,60]. 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 have produced results that suggest there is no significant differences between 24 versus 48 weeks of treatment [62]. 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 sub-group 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 attempt 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 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 Asian with HCV-1, especially given the higher SVR rates with both genotypes with PEG IFN+RBV in this ethnic group.

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List of Abbreviations

HCV	Hepatitis C Virus
SVR	Sustained Virological Response
PEG IFN+RBV	Pegylated Interferon and Ribavirin
AASLD	American Association for the Study of Liver Diseases
DDW	Digestive Disease Week
APASL	Asian Pacific Study of the Liver
EASL	European Association for the Study of the Liver
RCT	Randomized Controlled Trial
ITT	Intention-to-treat

EVR	Early Virological Response
OR	Odds Ratio

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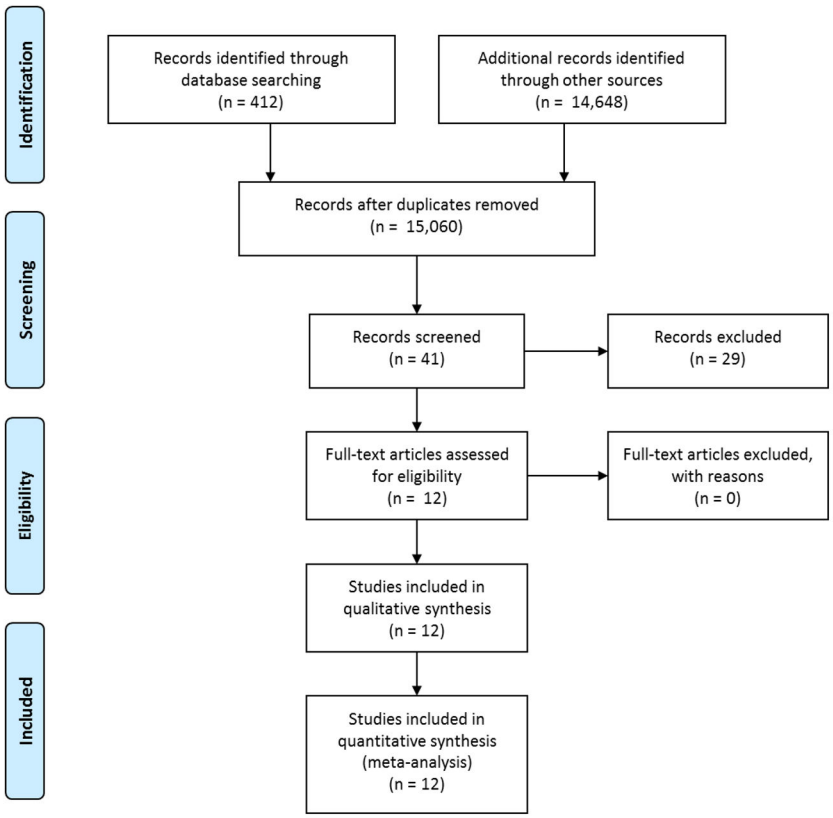

FIG. 1.
Flow diagram of studies identified and selected for inclusion into meta-analysis.

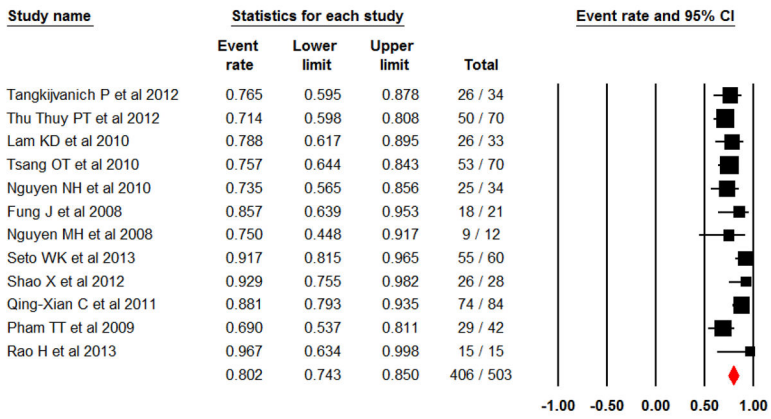

FIG. 2.

Pooled SVR rate in Asian patients with HCV genotype 6

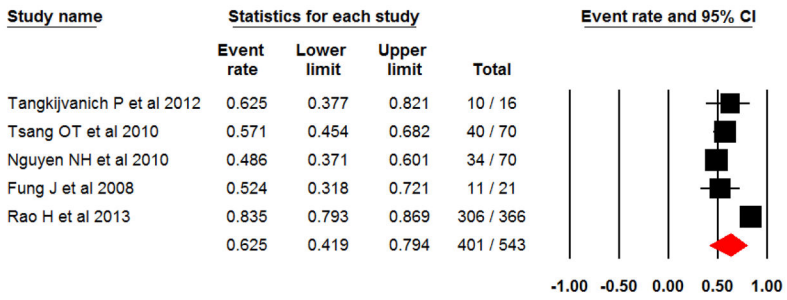

FIG. 3.

Pooled SVR rate in Asian patients with HCV genotype 1

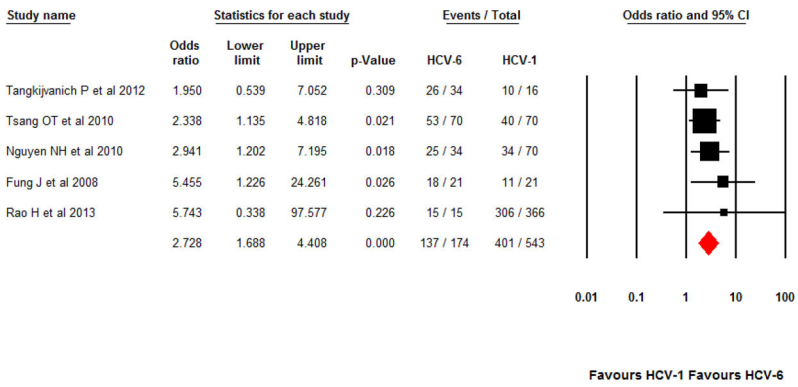

FIG. 4.

Pooled SVR rate between Asian patients with HCV-6 versus HCV-1 treated for 48 weeks

Table 1

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

Author	Population	HCV-6			HCV-1		
		males, n	age, years	n	males (%)	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 genotypes 6 and 1. n.a. = No data available.

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