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Sustained virological response and its treatment predictors in hepatitis C virus genotype 4 compared to genotypes 1, 2, and 3: a meta-analysis

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ABSTRACT

Background: Pegylated interferon and ribavirin (PEG-IFN+RBV) may be more cost-effective than direct-acting antivirals in resource-limited settings. Current literature suggests sustained virological response (SVR) in hepatitis C virus genotype 4 (HCV-4) is similar to genotype 1 (HCV-1), but worse than 2 and 3 (HCV-2/3). However, few studies have compared treatment response between these groups and these have been limited by small sample sizes with heterogeneous designs. We performed a meta-analysis of SVR predictors in HCV-4 versus HCV-1, 2, and 3 patients treated with PEG-IFN+RBV.

Methods: In November 2013, we searched for 'genotype 4' in MEDLINE/EMBASE databases and scientific conferences. We included original articles with ≥25 treatment-naïve HCV-4 and comparisons to HCV-1, 2, and/or 3 patients treated with PEG-IFN+RBV. Random effects modelling was used with heterogeneity defined by Cochrane Q-test (p value<0.10) and I^2 statistic (>50%).

Results: Five studies with 20 014 patients (899 HCV-4; 12 033 HCV-1; and 7082 HCV-2/3 patients) were included. SVR was 53% (CI 43% to 62%) for HCV-4, 44% (CI 40% to 47%) for HCV-1; and 73% (CI 58% to 84%) for HCV-2/3. SVR with EVR (early virological response) was 75% (CI 61% to 86%) in HCV-4; 64% (CI 46% to 79%) in HCV-1; and 85% (CI 71% to 93%) in HCV-2/3. SVR without EVR was 10% (CI 6% to 17%) for HCV-4; 13% (CI 12% to 15%) for HCV-1; and 23% (CI 16% to 33%) for HCV-2/3.

Conclusions: SVR rates are similar in HCV-4 (~50%) and HCV-1 (~40%). Lack of EVR is a good stopping rule for HCV-4 and HCV-1 since only 10% subsequently achieve SVR. In HCV-4 patients with EVR, three-quarters can expect to achieve SVR with PEG-IFN+RBV.

Summary box

What is already known about this subject?

- There are six major HCV genotypes (HCV-1 to HCV-6), which are geographically distributed and demonstrate variable response to antiviral treatment.
- While HCV-1, 2, and 3 have been well-represented in large registration trials, data on HCV-4 has been limited.
- Treatment guidelines recommend the same length of treatment with PEG-IFN+RBV in HCV-4 and HCV-1; however, there is conflicting published data regarding the rate of SVR in HCV-4 compared to HCV-1.

What are the new findings?

- In our meta-analysis of five studies with a total of 20 014 patients treated with PEG-IFN+RBV, we observed pooled SVR rates of 53% for HCV-4, 44% for HCV-1, and 73% for HCV-2/3.
- SVR was higher in HCV-2/3 compared to HCV-4 regardless of EVR status.
- SVR was similar in HCV-1 compared to HCV-4 regardless of EVR status.

How might it impact on clinical practice in the foreseeable future?

- With PEG-IFN+RBV, SVR rates of approximately 50% in HCV-4, 40% in HCV-1, and 70% in HCV-2/3 can be expected.
- Given the high cost of direct-acting agents, our data on patients treated with PEGIFN+RBV may help guide therapy in those who will only have access to IFN-based therapies.

BACKGROUND

Hepatitis C virus (HCV) is a worldwide health burden affecting approximately 170 million patients globally.[1–3] In about 40 000 patients each year, chronic infection leads to progressive liver scarring, end-stage liver disease or hepatocellular carcinoma.[4 5] These disease outcomes as well as response to therapy are influenced by HCV genotype.

There are six known HCV genotypes, which are geographically distributed. HCV-1 is the most prevalent worldwide, especially in the USA and Northern Europe, and is

responsible for approximately 70% of the global chronic hepatitis C (CHC) population.[6] In contrast, HCV-4 is more prominent in Africa and the Middle East, comprising up to 80% of the CHC burden in this region.[7]

Most registration trials with interferon-based therapies have been conducted in Western countries where HCV-1, 2, and 3 are prevalent, but data on other genotypes, especially HCV-4, is limited.[8 9] The goal of HCV treatment is to achieve sustained virological response (SVR), defined as undetectable HCV RNA at 24 weeks after cessation of therapy. While SVR rates have been firmly established in HCV-1, 2 and 3 by landmark clinical trials, the rate of SVR in HCV-4 has been wide-ranging from 28% to 71% based on smaller studies with heterogeneous designs mostly conducted in Africa and Eastern Mediterranean countries.[7 10–59]

Guidelines recommend the same 48-week treatment duration with PEG-IFN+RBV for HCV-4 and HCV-1, based on the assumption that these genotypes have similar SVR rates. While some studies comparing HCV-4 and HCV-1 have shown no difference in SVR rates between these genotypes,[42 43 46] others have shown a trend favouring higher SVR rates for HCV-4 patients compared to HCV-1 patients.[14 32] Additional research is needed to better our understanding of HCV-4 and HCV-1 since these two genotypes may be considered as separate entities and ultimately require different treatment considerations.

The aim of our study is to systematically and qualitatively assess treatment predictors and outcomes in studies directly comparing patients with HCV-4 and HCV-1, 2, and/or 3 who were treated with PEG-IFN +RBV.

METHODS

Data sources and searches

In November 2013, we performed a literature search in PubMed filtered for MEDLINE-indexed articles with the search term: ('genotype 4'). Studies in non-English languages were included. We also performed a literature search in EMBASE with the search term: 'hepatitis c'/exp, and conducted a manual review of abstracts using the search term 'genotype 4' for all recent international gastroenterology and liver society meetings held between 2012 and 2013, which included the American Association for the Study of Liver Diseases (AASLD), Asian Pacific Study of the Liver (APASL), Digestive Disease Week (DDW) and European Association for the Study of the Liver (EASL).

Study selection

Inclusion criteria were original studies with a minimum sample size of ≥25 treatment-naïve, HCV-4 and comparison treatment arm of HCV-1, 2, and/or 3 patients, all of whom received treatment with PEG-IFN+RBV. Both prospective controlled trials and retrospective cohort reports were eligible for inclusion. Exclusion criteria were patients coinfected with hepatitis B or D, HIV or other liver diseases. Two of the study authors (BEY and BZ) evaluated the studies independently, and a third author (MHN) re-reviewed these articles. Any discrepancies were resolved by consensus.

Data extraction

The study team developed a data abstraction form for this meta-analysis. Information collected from studies were the following: (1) study characteristics including year published, country of origin, study design, study type (randomised-controlled trial vs observational), practice setting (university or community), and intention-to-treat (ITT) analysis; (2) patient characteristics including age, gender, ethnicity, degree of fibrosis, viral load, and ALT level; (3) treatment predictors including length of treatment (24-weeks compared to 48-weeks), rates of rapid virological response (RVR, defined as undetectable HCV RNA at week 4 of treatment) and early virological response (EVR, defined as at least 2-log 10 reduction of HCV RNA from baseline at week 12 of treatment); (4) rates of SVR (SVR, defined as undetectable HCV RNA at 24 weeks after cessation of treatment).

Statistical analysis

Statistical analyses were performed using random effects modelling (DerSimonian and Laird method) and inverse variance method[60] to present pooled event rates (overall SVR rate) with corresponding 95% CIs. Study heterogeneity was assessed using χ^2-based Cochrane Q-statistic with $p \leq 0.10$ and $I^2 \geq 50\%$ as per the standards of quality for reporting meta-analysis from the Cochrane handbook.[60] For subgroup analyses, ORs and corresponding 95% CIs were performed. Funnel plots of ln[OR] against SE were performed to evaluate for publication bias. One-study removed influence analysis was conducted to identify potential outliers contributing to our pooled estimates. A fixed value of '0.5' was added to all cells of study results tables in studies with zero-cell counts.[60] Statistical tests were all two sided. All statistical tests were performed using Comprehensive Meta-Analysis, V.2 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search

As shown in figure 1, a comprehensive literature review of PubMed and EMBASE identified 1798 studies. Review of scientific conferences held in the past 2 years identified 14 648 abstracts. Based on abstract and article titles, a total of 16 446 studies were not relevant and excluded prior to screening. Eighty-four studies were closely reviewed.[7 10–59 61–93] A total of 79 studies were excluded for the following reasons: 45 studies did not have direct comparison arms of HCV-1, 2, and/or 3;[7 10–13 15–31 33–39 41 44 45 47–59] 14 studies did not have accessible treatment outcomes data;[61 62 67 70 72 76 78 79 82 84 85 87 92 93] 6 studies were redundant;[71 73 75 80 86 91] 4 studies were not relevant;[63 68 77 88]

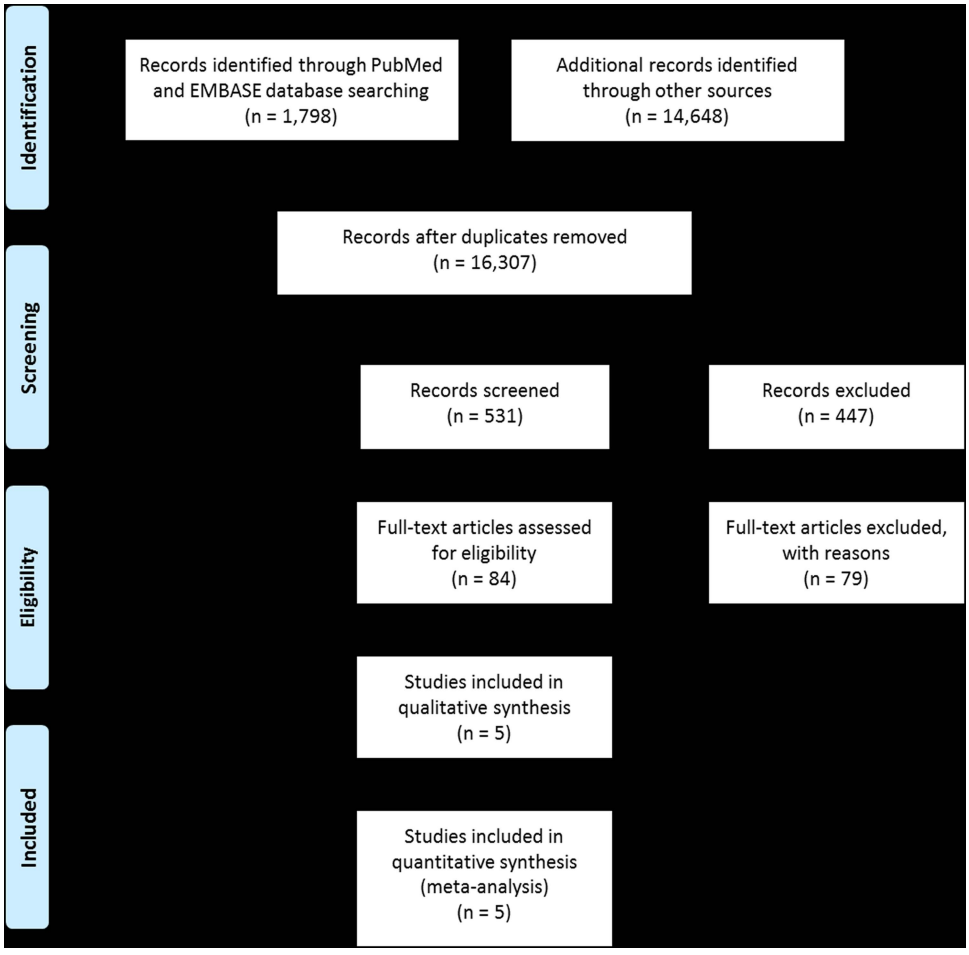

Figure 1 PRISMA flow diagram of articles identified and screened for inclusion.

3 studies included patients coinfected with other conditions, including hepatitis B virus, HIV or other liver diseases;[69 81 83] 3 studies did not assess treatment-naïve patients;[64 65 89] 2 studies did not contain original data;[74 90] 1 study did not meet our minimum sample size requirement of at least 25 HCV patients;[66] 1 study did not include patients treated for 48 weeks.[40] A total of five studies met all eligibility criteria and were included in the primary analysis.[14 32 42 43 46]

Characteristics of included studies and patients

Five full-length articles with a total of 20 014 patients (899 HCV-4; 12 033 HCV-1; and 7082 HCV-2/3 patients) were included in this meta-analysis (table 1). All were observational or non-randomised. Four studies were prospective[32 42 43 46] while one was retrospective in design.[14] Four of the five studies analysed SVR rates according to ITT.[14 32 42 43] Study origins included two from Kuwait,[14 32] one from Germany[43] and one from Cameroon.[46] One study was conducted in 19 countries.[42] The majority of patients were male. Mean age ranged from 44.5 to 54.3 years for HCV-4; 47.4 to 53 years for HCV-1; and 46.3 to 51.4 years for HCV-2/3. This analysis only included patients treated with PEG-IFN+RBV.

SVR rates by genotype

Based on five studies, pooled SVR rate for HCV-4 was 52.7% (CI 43.4% to 61.9%) (Q-statistic=21.04, p<0.001, I^2=80.99%) (table 2). Corresponding pooled SVR rates for HCV-1 and HCV-2/3 were 43.7% (CI 40.3% to 47.1%) (Q-statistic=17.696, p=0.001, I^2=77.40%) and 72.9% (CI 58.5% to 83.7%) (Q-statistic=190.997, p<0.001, I^2=98.43%), respectively. Statistically significant heterogeneity was found in the analysis of each genotype and this may be attributed to variation in the patient characteristics and methodologies among the included studies.

SVR rates in HCV-4 and HCV-1 were comparable, detecting no statistically significant difference, OR 1.16 (CI 0.92 to 1.48, p=0.21) (Q-statistic=6.264, p=0.18, I^2=36.14%). In contrast, the rate of SVR in HCV-2/3 was higher than HCV-4, OR 2.74 (CI 1.55 to 4.85, p=0.01) (Q-statistic=21.046, p<0.001, I^2=85.75%) as well as HCV-1, OR 3.33 (CI 1.89 to 5.87, p<0.001) (Q-statistic=90.944, p<0.001, I^2=96.70%).

Treatment predictors of SVR by genotype

Rapid virological response

Two studies provided data on RVR for a total of 12 982 patients.[42 43] Pooled rates of RVR were 39.3% (CI 35.3%

Table 1 Characteristics of studies included in primary analysis

			HCV-4			HCV-1			HCV-2/3		
First author, year	Country of origin	Study design	Male (%)	Age (years)	N	Male (%)	Age (years)	N	Male (%)	Age (years)	N
Marcellin P *et al*, 2012[42]	International (19 countries)	Prospective	68	44.5	282	52	47.4	4119	60	46.3	1976
Mauss S *et al*, 2012[43]	Germany	Prospective	76	Median 41	474	60	Median 44	7835	66	Not reported	5062
Al-Enzi SA *et al*, 2011[14]	Kuwait	Retrospective	Not reported	Not reported	51	Not reported	Not reported	30	Not reported	Not reported	27
Njouom R *et al*, 2008[46]	Cameroon	Prospective	71	54.3	26	82	53	29	86	51.4	17
Hasan F *et al*, 2004[32]	Kuwait	Prospective	73	45	66	35	48	20	Not reported	Not reported	Not reported

HCV, hepatitis C virus.

to 43.5%) (Q-statistic=0.452, p=0.501, I^2=0.00%) in 552 patients with HCV-4; 24.8% (CI 23.9% to 25.8%) (Q-statistic=0.131, p=0.717, I^2=0.00%) in 8173 patients with HCV-1; and 75.9% (CI 71.2% to 80.0%) (Q-statistic=11.735, p=0.001, I^2=91.48%) in 4257 patients with HCV-2/3.

Direct comparison of RVR rates detected statistically significant differences favouring HCV-2/3 over HCV-4, OR 4.85 (CI 3.40 to 6.94, p<0.001) (Q-statistic=3.732, p=0.053, I^2=73.21%), and HCV-4 over HCV-1, OR 1.96 (CI 1.64 to 2.35, p<0.001) (Q-statistic=0.295, p=0.59, I^2=0.00%).

Early virological response

In four studies, pooled rates of EVR were 72.8% (CI 63.5% to 80.5%) for 695 patients with HCV-4 and 91.4% (CI 88.8% to 93.4%) for 5568 patients with HCV-2/3.[14 42 43 46] In three studies, pooled rate of EVR was 59.4% (CI 57.9% to 60.9%) for 4178 patients with HCV-1.[14 42 46]

Direct comparison of EVR rates detected a statistically significant difference favouring HCV-2/3 over HCV-4, OR 3.53 (CI 1.81 to 6.87, p<0.001) (Q-statistic=17.820, p<0.001, I^2=83.16%), but did not detect any statistically significant difference between HCV-4 and HCV-1, OR 1.46 (CI 0.88 to 2.43) (Q-statistic=3.119, p=0.21, I^2=35.88%).

SVR in patients who achieved EVR

Regarding the rate of SVR in patients who achieved EVR, three studies[14 42 46] provided data on HCV-1 and HCV-2/3 while four studies[14 32 42 46] provided data on HCV-4. The pooled rates of SVR in those who achieved EVR were 75.4% (CI 61.4% to 85.6%) in 300 HCV-4 patients; 64% (CI 46.4% to 78.6%) in 2481 HCV-1 patients; and 85.2% (CI 71.8% to 92.9%) in 1876 HCV-2/3 patients.

As shown in figure 2, direct comparison of SVR rates detected a statistically significant difference favouring HCV-2/3 over HCV-4 in patients who achieved EVR, OR 2.33 (CI 1.71 to 3.16, p<0.001) (Q-statistic=0.442, p=0.802, I^2=0.00%). No statistically significant difference was found between HCV-4 and HCV-1 patients who reached EVR, OR 1.29 (CI 0.52 to 3.19) (Q-statistic=4.701, p=0.095, I^2=57.45%).

SVR in patients who did not reach EVR

Regarding the rate of SVR in patients who did not reach EVR, four studies[14 32 42 46] provided data on HCV-4 while three studies provided data on HCV-1 and HCV-2/3.[14 42 46] The pooled rates of SVR in those who did not reach EVR were 10% (CI 5.7% to 16.6%) in 127 HCV-4 patients; 13.1% (CI 11.6% to 14.8%) in 1698 HCV-1 patients; and 22.3% (CI 16.6% to 30.2%) in 146 HCV-2/3 patients.

As shown in figure 3, direct comparison of SVR rates detected a statistically significant difference favouring HCV-2/3 over HCV-4 in patients who did not reach EVR, OR 2.75 (CI 1.28 to 5.92, p=0.01) (Q-statistic=0.64, p=0.969, I^2=0.00%). No statistically significant difference was found between HCV-4 and HCV-1 patients who did

Table 2 Treatment response in HCV-4 compared to HCV-1 and HCV-2/3

Treatment response	HCV-4 (n=899)	HCV-1 (n=12 033)	HCV-2/3 (n=7082)
SVR	53% (CI 43% to 62%)	44% (CI 40% to 47%)	73% (CI 58% to 84%)
RVR	39% (CI 35% to 44%)	25% (CI 24% to 56%)	76% (CI 71% to 80%)
EVR	72% (CI 64% to 81%)	59% (CI 58% to 61%)	91% (CI 89% to 93%)
+EVR/+SVR	75% (CI 61% to 86%)	64% (CI 46% to 79%)	85% (CI 71% to 93%)
−EVR/+SVR	10% (CI 6% to 17%)	13% (CI 12% to 15%)	23% (CI 16% to 33%)

EVR, early virological response; HCV, hepatitis C virus; RVR, rapid virological response; SVR, sustained virological response.

not reach EVR, OR 0.72 (CI 0.37 to 1.43) (Q-statistic=0.178, p=0.915, I^2=0.00%).

DISCUSSION

In our primary analysis, we included five studies with a total of 20 014 patients (899 HCV-4; 12 033 HCV-1; and 7082 HCV-2/3). We observed pooled SVR rates of 53%, 44%, and 73% in patients with HCV-4, HCV-1 and HCV-2/3, respectively. While SVR rates with HCV-2/3 patients were significantly higher than HCV-4, we found no statistically significant difference between SVR rates with HCV-1 patients compared to HCV-4.

Prior guidelines from EASL in 2013[94] and AASLD in 2009[5] recommended dual therapy with PEG-IFN+RBV for HCV-4 carriers. Both societies' recommendations for response guided therapy combined recommendations for HCV-4 with HCV-1. Beginning in 2011, telaprevir and boceprevir were the first new direct-acting antivirals (DAA) licensed for use in HCV-1. Currently there are several other DAAs available, including sofosbuvir, simeprevir, sofosbuvir/ledipasvir, and paritaprevir/ritonavir/ombitasvir, which are approved for HCV-1 and HCV-4.[95–97] With shorter treatment duration and higher potency, triple therapy has significantly improved virological response rates for many HCV-infected individuals. However, this therapeutic option may remain elusive for patients in developing or under-resourced regions who lack access to DAAs. Therefore, dual therapy with PEG-IFN+RBV will likely remain the mainstay of treatment for many CHC patients in developing countries and is still a treatment option in the WHO guidelines.[98]

Although societies have grouped HCV-4 with HCV-1, there has been conflicting data as some studies showed a trend towards higher SVR rates in HCV-4 compared to HCV-1,[14 32] whereas other studies have not demonstrated any significant differences.[42 43 46] In our meta-analysis of studies directly comparing HCV-4 and HCV-1 patients, HCV-4 patients had significantly higher rates of RVR (OR 1.96, CI 1.64 to 2.35, p<0.001), but no statistically significant difference in SVR rates (53% vs 44%, OR 1.16 (CI 0.92 to 1.48, p=0.21)). Additionally, when compared to patients with HCV-2/3, patients with HCV-4 and HCV-1 both had lower rates of RVR, EVR and SVR.

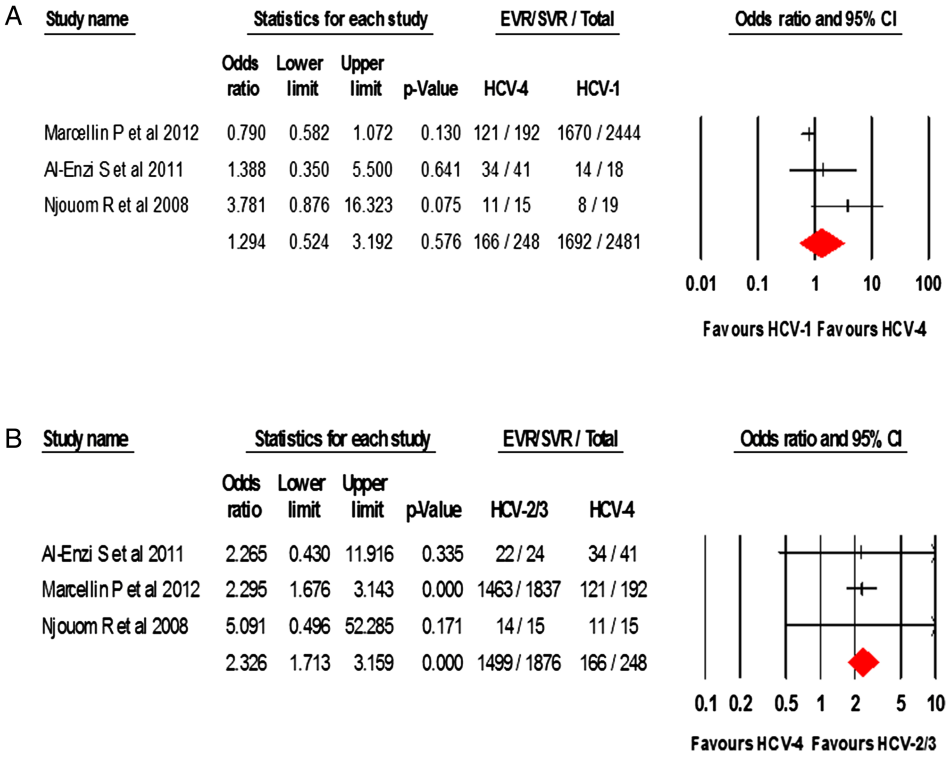

Figure 2 Odds of SVR with EVR in HCV-4 compared to (A) HCV-1 or (B) HCV-2/3. EVR, early virological response; HCV, hepatitis C virus; SVR, sustained virological response.

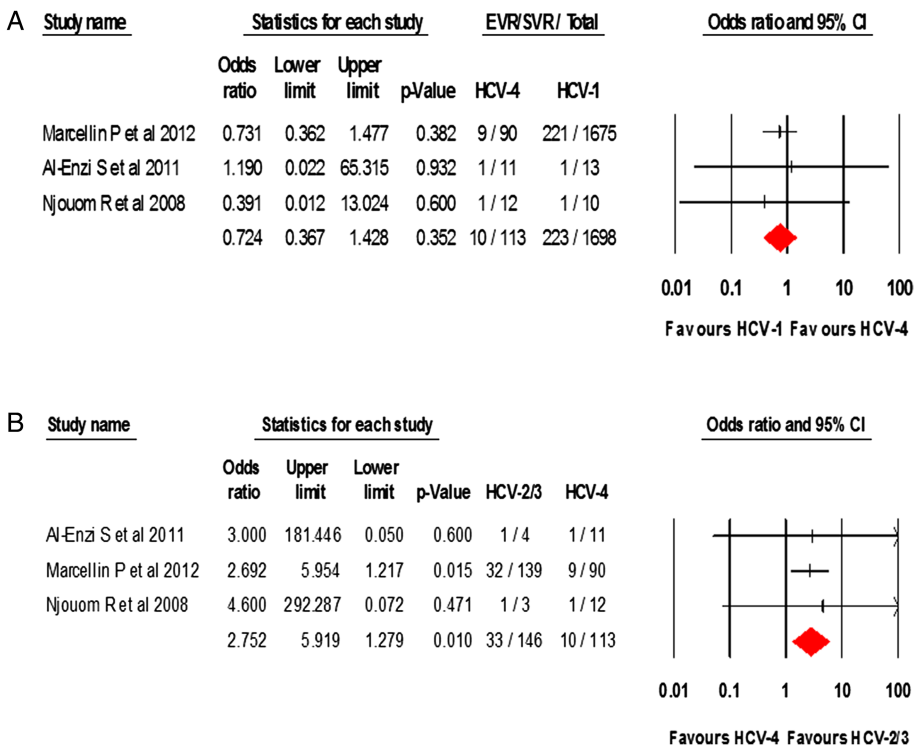

Figure 3 Odds of SVR without EVR in HCV-4 compared to (A) HCV-1 or (B) HCV-2/3. EVR, early virological response; HCV, hepatitis C virus; SVR, sustained virological response.

Our findings are similar to results from large randomised controlled trials of PEG-IFN+RBV treatment.[8 9] However, the generalisability of these previous trials has been limited due to the paucity of HCV-4, which represented less than 41 patients or 3% of the total subjects randomised to treatment with PEG-IFN+RBV. In contrast, the current meta-analysis includes 899 HCV-4 patients from studies, which also provided comparison data for other treated genotype(s). To our knowledge, this is the first meta-analysis comparing virological response in HCV-4 to HCV-1 and HCV-2/3 patients treated with PEG-IFN+RBV. Subgroup analysis included only observational or non-randomised studies since no large RCTs with sufficient numbers of HCV-4, HCV-1 and/or HCV-2/3 patients have been performed. In the absence of any large RCTs comparing these genotypes, this meta-analysis provides the largest sample of HCV-4, HCV-1 and HCV-2/3 patients with a direct comparison of their SVR rates.

In the secondary analysis of treatment predictors, RVR rates were 39.3% in HCV-4, 24.8% in HCV-1 and 75.9% in HCV-2/3. Prior estimates of RVR in all genotypes have ranged widely: 15%–60% in HCV-4,[7 16 17 24 34 38 42–44 58 65 99] 20%–45% in HCV-1,[99–103] and 60%–95% in HCV-2/3,[99 101 102 104–107] which may be due in part to demographic or epidemiological factors as well as the distribution of advantageous *IL28B* phenotypes, which were not assessed by the studies included in this analysis. In direct comparison, RVR was favoured in HCV-2/3 over HCV-4, OR 4.85 (CI 3.40 to 6.94, p<0.001) and HCV-4 over HCV-1, OR 1.96 (CI 1.64 to 2.35, p<0.001), a finding previously reported in the current literature.

With both AASLD and EASL guidelines, EVR is especially important for response-guided therapy as failure to achieve EVR is used to recommend discontinuation of therapy at week 12 of therapy. In our study, overall EVR rates were 72.8% in HCV-4, 59.4% in HCV-1, and 91.4% in HCV-2/3. SVR rates in those who achieved EVR were 75.4% in HCV-4, 64% in HCV-1 and 85.2% in HCV-2/3. In contrast, SVR rates in those who did not reach EVR were 10% in HCV-4, 13.1% in HCV-1, and 22.3% in HCV-2/3. Failure to achieve EVR was a negative predictor of response to treatment for all genotypes.

As with HCV-1, lack of EVR is a good stopping rule for HCV-4 given the low SVR rate in those without EVR in the current meta-analysis and supports the societal recommendations that group HCV-4 with HCV-1. In addition, continuing therapy in HCV-4 patients who achieve EVR is also important as approximately three-quarter of HCV-4 patients treated with PEG-IFN+RBV achieved EVR and of those patients, three-quarters achieved SVR.

Although our meta-analysis is the first to quantitatively evaluate treatment predictors and outcomes in such a large population of patients with HCV-4, HCV-1, or HCV-2/3, this study was not without its limitations. Data on newer, all-oral regimens was not included. Additionally, only a small number of studies with a significant amount of heterogeneity were available for this analysis, which limited our ability to perform any additional subgroup analyses or detect publication bias. Our comprehensive literature search yielded only observational or non-randomised studies. Although randomised controlled trials are the reference standard, the studies included in

this analysis may be more generalisable to routine clinic settings of heterogeneous patient populations.

In summary, in this meta-analysis of PEG-IFN+RBV treated patients, we observed a higher SVR rate in HCV-2/3 (~70%) and comparable SVR rates in HCV-4 (~50%) and HCV-1 (~45%). As in HCV-1, failure to achieve EVR may be a good stopping rule for patients with HCV-4. Considering the lower SVR rates in HCV-4 and HCV-1, HCV-4 patients infected with these genotypes may significantly benefit from the recently FDA-approved triple therapies, where available. In more resource limited regions, given the higher rate of RVR (39%) and EVR in HCV-4 patients (73%) compared to HCV-1 patients (25% and 59%, respectively) and high SVR in those with EVR (75%), a response-guided approach using PEG IFN+RBV is probably still a reasonable option for the majority of patients. As hepatitis C treatment rapidly evolves, future trials may benefit from use of more diverse patient populations to improve the representation of less common genotypes.

Contributors MHN was guarantor of the article. BEY was involved in the study design, data collection, data analysis and interpretation and drafting of the manuscript. BZ and NHN were involved in the study design, data collection, data analysis and interpretation and participation in the drafting of the manuscript. PV and CRW were involved in the data collection and critical review of the manuscript. DL and GAL were involved in the data interpretation and critical review of the manuscript. MHN was involved in the 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.

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Competing interests MHN has served as a consultant and an advisory board member for Gilead Sciences Inc., Bristol-Myers Squibb, Novartis, and Bayer.

Patient consent Obtained.

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