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 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.In November 2013, we searched for genotype 4 in MEDLINE/EMBASE databases and scientific conferences. We included original articles with 25 treatment-nave 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 value50%).Five studies with 20014 patients (899 HCV-4; 12033 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.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.Keywords: HEPATITIS C, GENOTYPE, HCVThere 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.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.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.Hepatitis C virus (HCV) is a worldwide health burden affecting approximately 170 million patients globally.13 In about 40000 patients each year, chronic infection leads to progressive liver scarring, end-stage liver disease or hepatocellular carcinoma.45 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.7Most 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.89 The goal of HCV treatment is to achieve sustained virological response (SVR), defined as undetectable HCV RNA at 24weeks 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.71059Guidelines 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,424346 others have shown a trend favouring higher SVR rates for HCV-4 patients compared to HCV-1 patients.1432 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.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).Inclusion criteria were original studies with a minimum sample size of 25 treatment-nave, 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.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 24weeks after cessation of treatment).Statistical analyses were performed using random effects modelling (DerSimonian and Laird method) and inverse variance method60 to present pooled event rates (overall SVR rate) with corresponding 95% CIs. Study heterogeneity was assessed using 2-based Cochrane Q-statistic with p0.10 and I250% 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 tablesin 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).As shown in figure 1, a comprehensive literature review of PubMed and EMBASE identified 1798 studies. Review of scientific conferences held in the past 2years identified 14648 abstracts. Based on abstract and article titles, a total of 16446 studies were not relevant and excluded prior to screening. Eighty-four studies were closely reviewed.710596193 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;7101315313339414454759 14 studies did not have accessible treatment outcomes data;6162677072767879828485879293 6 studies were redundant;717375808691 4 studies were not relevant;63687788 3 studies included patients coinfected with other conditions, including hepatitis B virus, HIV or other liver diseases;698183 3 studies did not assess treatment-nave patients;646589 2 studies did not contain original data;7490 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 48weeks.40 A total of five studies met all eligibility criteria and were included in the primary analysis.1432424346 PRISMA flow diagram of articles identified and screened for inclusion.Five full-length articles with a total of 20014 patients (899 HCV-4; 12033 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 prospective32424346 while one was retrospective in design.14 Four of the five studies analysed SVR rates according to ITT.14324243 Study origins included two from Kuwait,1432 one from Germany43 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 54.3years for HCV-4; 47.4 to 53years for HCV-1; and 46.3 to 51.4years for HCV-2/3. This analysis only included patients treated with PEG-IFN+RBV.Characteristics of studies included in primary analysisFirst author, yearCountry of originStudy designHCV-4HCV-1HCV-2/3Male (%)Age (years)NMale (%)Age (years)NMale (%)Age (years)NMarcellin P et al, 201242International (19 countries)Prospective6844.52825247.441196046.31976Mauss S et al, 201243GermanyProspective76Median 4147460Median 44783566Not reported5062Al-Enzi SA et al, 201114KuwaitRetrospectiveNot reportedNot reported51Not reportedNot reported30Not reportedNot reported27Njouom R et al, 200846CameroonProspective7154.3268253298651.417Hasan F et al, 200432KuwaitProspective734566354820Not reportedNot reportedNot reportedBased on five studies, pooled SVR rate for HCV-4 was 52.7% (CI 43.4% to 61.9%) (Q-statistic=21.04, p