Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Romero-Gomez M. et al. (2013) Meta-analysis: pegylated interferon alpha-2a achieves higher early virological responses than alpha-2b in chronic hepatitis C. *Alimentary Pharmacology & Therapeutics*, 37(11):1065-1073.
Date of Review:	March 2, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **people infected with hepatitis C virus** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Spain** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Meta-analysis; comparison of the rapid virological response and early virological response of peginterferon α-2a vs. peginterferon α-2b treatment in people with chronic hepatitis C
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Primary outcome: rapid virological response rate, defined by seronegativity of HCV RNA at 4 weeks of treatment; and complete early virological response, defined by undetectable HCV RNA within initial 12 weeks of treatment

Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	8 studies with 4566 patients included in the analysis
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Literature search using MEDLINE, EMBASE, LILACS and Cochrane Central Register of Controlled Trials.
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology was clearly described
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	similar analysis can be done through implementing the same inclusion criteria
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Alimentary Pharmacology & Therapeutics*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Free to download from http://onlinelibrary.wiley.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	

How is the best practice/intervention funded? ***Please got to Comments section***	☒	☐	☐	Editorial services provided by Dr Blanca Piedrafita were supported by a grant from Roche Farma S.A.
Other relevant information: _____	☐	☐	☐	- Peg-INF α-2a may be associated with higher RVR and cEVR than Peg-INF α-2b

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: pegylated interferon α-2a achieves higher early virological responses than α-2b in chronic hepatitis C

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SUMMARY

Background
A Cochrane meta-analysis established that pegylated interferon α-2a is more effective than peginterferon α-2b in terms of sustained virological response (SVR) in the treatment of chronic hepatitis C. Rapid virological response (RVR) and early virological response (EVR) are crucial to reach SVR and to make clinical decisions.

Aim
To compare RVR and EVR rates of peginterferon α-2a vs. peginterferon α-2b through a meta-analysis of previously published randomised control trials (RCT).

Methods
MEDLINE, EMBASE and LILACS databases were systematically searched up to September 2011. Seven RCT that reported complete early virological response (cEVR) were selected. A meta-analysis focusing on RVR and cEVR outcomes was conducted and Relative Efficacy (RE) was calculated.

Results
Meta-analysis of cEVR included seven trials (n = 4359), and yielded an estimated effect in favour of peginterferon α-2a: Crude Efficacy (CEf) was 53.3% vs. 43.8%, RE = 1.118 (CI 95% = 1.039–1.203; P = 0.0028), heterogeneity Q = 8.959; I^2 = 33.0% (P = 0.1759). A sub-analysis of three studies with 3409 genotype-1 patients yielded CEf: 49.4% vs. 40.2%, RE = 1.151 (CI 95% = 0.968–1.369; P = 0.1124), Q = 9.802; I^2 = 79.6% (P = 0.0074). Meta-analysis of RVR included five trials (n = 3833) with an estimated effect in favour of peginterferon α-2a: CEf = 25.0% vs. 16.8%, RE = 1.151 (CI 95%:1.042–1.272; P = 0.0056), Q = 1.461; I^2 = 0.0% (P = 0.8335). Analysis of four studies reporting RVR including 3499 patients with genotypes 1 and 4 resulted in CEf: 18.3% vs. 12.7% RE = 1.206 (CI 95% = 1.059–1.374; P = 0.0048), Q = 1.116; I^2 = 0.0% (P = 0.7733).

Conclusions
Peginterferon α-2a may be associated with a higher cEVR and RVR than peginterferon α-2b. These findings could help to achieve higher SVR rates and support clinical decision-making in the present scenario of triple combination therapy.

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BACKGROUND

Chronic hepatitis C can progress to cirrhosis, liver failure or liver cancer. In fact, in the Western world, chronic hepatitis C is the major cause of cirrhosis, and contributes to the incidence of hepatocellular carcinoma.[1] Its treatment has evolved in the past decade; the use of interferon was initially complemented with the guanosine nucleoside ribavirin (RBV), and then later by binding of interferon α with polyethylene glycol. This prolongs its half-life, modifies its pharmacokinetic, pharmacodynamic and immunological properties,[2, 3] and increases the sustained virological response (SVR) to 50%, leading to its recommendation as first-line treatment in hepatitis C virus (HCV) chronic infection.[4] However, about 50% of treated patients are non responders or relapsers, and the response rate varies according to HCV genotype. HCV genotypes 2 and 3 are more responsive to therapy than genotype 1, having comparatively higher SVR rates if treated with the same strategy.[5] Thus, HCV genotype has to be considered in the treatment indication, dose, duration and virological monitoring procedure.

Two forms of pegylated interferon are currently available: peginterferon α-2a (Pegasys®; Hoffmann-LaRoche, Basel, Switzerland) and peginterferon α-2b (PegIntron®; Schering-Plough, Kenilworth, NJ, USA), but have significant differences in terms of pharmacokinetics and pharmacodynamics.[5–8] Studies have also been conducted to establish the different therapy profiles of these two peginterferons.[2, 9–17] However, a recent Cochrane meta-analysis established that pegylated interferon α-2a is more effective than pegylated interferon α-2b in terms of SVR in the treatment of chronic hepatitis C.[18] Although SVR is considered to be the most clinically important rate, the rapid virological response (RVR)[19] and quantification of HCV RNA at week 4 and week 12 (complete early virological response; cEVR)[19] are crucial for making clinical decisions, as they predict the SVR and provide clinicians with useful and early information to decide on the most appropriate approach. In the present clinical scenario, RVR and cEVR enable response-guided therapy to be applied (e.g. initiating triple therapy in patients achieving or not achieving RVR, because a protease inhibitor is not used during this period). At present, boceprevir and telaprevir (two drugs that are used in combination with peginterferon and RBV) are available for G1 patients. This combination significantly improves SVR rates. Thus, RVR is essential for the management of hepatitis C patients in the triple therapy era. Moreover, early outcome measures may also lead to discontinuing treatments when the patient does not experience any benefits, nor are they expected to, avoiding the extra costs and adverse effects of unsuccessful treatment. Consequently, selection of the appropriate interferon could determine whether RVR, cEVR and ultimately SVR are reached in triple therapy approaches, which may translate into more cost-effective treatments.

We performed a meta-analysis of available randomised controlled trials comparing peginterferon α-2a and α-2b to explore the outcome in terms of RVR and cEVR.

METHODS

Literature search

A systematic literature search with predefined search terms was carried out in MEDLINE, EMBASE, LILACS and the Cochrane Central Register of Controlled Trials for articles and abstracts up to September 2011. The keywords used and combined were 'polyethylene glycol-interferon α-2b, PEG-IFN α-2b, pegylated interferon α-2b, PEG IFN α-2b, PEG IFN α-2b, Pegintron, ViraferonPeg, PEG-Intron, PEG-IFN α-2A, PEG-interferon α-2A, polyethylene glycol-interferon α-2A, PEG-IFN α-2A, Pegasys, Hepatitis C and HCV'. The search was limited to human subjects, adults and randomised clinical trials (RCT). Further trials were identified by searching conference abstracts and the bibliography of studies considered to be relevant.

Study selection

Our review included randomised, prospective studies that evaluated standard combination therapy with pegylated interferon and ribavirin, with or without protease inhibitors, in HCV-infected patients. Thus, our population was of chronic hepatitis C patients, the intervention arm was pegylated interferon α-2a and the comparison arm was pegylated interferon α-2b. Eligibility criteria were RCT that included HCV-infected adults (>18 years) treated with pegylated interferon α-2a or 2b and ribavirin, with or without a protease inhibitor. Only studies with data on cEVR and RVR rates were considered. RCT including patients with human immunodeficiency virus or hepatitis B virus co-infection, haemophilia, decompensated liver cirrhosis, hepatocellular carcinoma and liver or renal transplantation were excluded.

Data extraction

All retrieved records and full-text articles were examined independently by two authors to identify those

RCTs that satisfied our inclusion criteria. Analysis data from the selected RCTs were extracted using a data collection form with the following fields: randomisation time point, duration of treatment, number of participants per treatment arm, HCV genotypes included, dosages of peginterferon and ribavirin and type of peginterferon, end of treatment, cEVR and RVR. The quality of the RCTs was assessed using the Jadad scale.[20]

Endpoints of interest

The primary outcomes of interest were the RVR rate (seronegativity of HCV RNA 4 weeks from initiation of treatment) and cEVR (undetectable HCV RNA within the initial 12 weeks of treatment).[19]

Statistical analyses

The effect of both management strategies on RVR and cEVR rates in HCV patients were analysed considering a dichotomised response to treatment. The Relative Efficacy (RE) and 95% confidence interval (CI) were calculated. We used the weighting inverse variance and random effects model based on DerSimonian's methodology.[21] Overall efficacy was established with QA (Q of association) and heterogeneity with Q, both with a Chi-square distribution to calculate statistical significance.[22] I^2 was also calculated as complementary information for heterogeneity. $I^2 < 25\%$ was considered low heterogeneity, $I^2 < 50\%$ moderate heterogeneity and $I^2 < 75\%$ high heterogeneity. Publication bias was estimated by examination of asymmetry in funnel plots. Relative Efficacy values higher than 1 indicate greater efficacy of peginterferon-α2a. The selected studies were reviewed individually to ensure that all fulfilled the inclusion criteria, and to identify possible significant biases within studies.

Non commercial software developed by the Autonomous University of Barcelona was used to perform statistical analyses, and manual calculations were performed to complement the analysis.

RESULTS

We originally identified 13 RCT satisfying our inclusion criteria, but five were finally discarded, as they failed to report all the information of interest. The pooled number of patients in these studies comparing peginterferon-α2a plus weight-based RBV vs. peginterferon α-2b plus weight-based RBV was 4566. Five of the studies reported RVR[2, 12–14, 23] and seven reported cEVR.[2, 9, 10, 13, 14, 23, 24] One triple therapy study that compared both pegylated interferons together with RBV and telaprevir was also included.[23] Figure 1 shows the results of the study screening. Table 1 summarises the general characteristics of the selected studies; table 2 shows the Jadad results used to assess their quality. Six of eight studies scored higher than 3, indicating overall good quality. The ribavirin dose was weight-based in all trials, ranging from 800 to 1400 g/day. HCV genotype in the selected trials varied, but five studies included patients with all four most prevalent genotypes. These studies generally included treatment-naïve patients, except one performed with non responders.[21] Five trials reported results according to HCV genotype, which allowed further sub-analysis in this study.[2, 12–14, 23] With respect to the methodological quality of the selected trials, none were discontinued early and adhered to the intention-to-treat principle. All except one[10] were clear with respect to blinding processes regarding allocation concealment, but only one was clearly defined as a double-blind trial.[9] Loss of follow-up was proportional to sample size.

Our cEVR meta-analysis included seven trials and 4359 patients (Figure 2). This analysis showed an overall significant increase in the percentage of patients treated with peginterferon α–2a that achieved cEVR (Crude Efficacy, [CEf] = 53.3%) when compared with the peginterferon α-2b group (43.8%), RE = 1.118, 95% CI = 1.039–1.203 ($P = 0.0028$). The Q parameter for heterogeneity in this analysis was 8.959, $I^2 = 33.0\%$ ($P = 0.1759$). A sub-analysis considering only patients infected with HCV genotypes 1 and 4 was performed, and included three studies (3409 patients) that reported separate outcomes for these two genotypes; the results were CEf = 49.4% and 40.2% for peginterferon α-2a and peginterferon α-2b, respectively, RE = 1.151; 95% CI = 0.968–1.369 ($P = 0.1124$). The heterogeneity test yielded $Q = 9.802$, $I^2 = 79.6\%$ ($P = 0.0074$). Meta-analysis of RVR included five trials and 3833 patients, with an estimated effect in favour of peginterferon α-2a of 25.0% crude efficacy vs. 16.8% for peginterferon α-2b (RE = 1.151, 95% CI = 1.042–1.272, $P = 0.0056$), heterogeneity $Q = 1.461$ and $I^2 = 0.0\%$ ($P = 0.8335$). Our results for the sub-analysis of genotypes 1 and 4, with four studies (3499 patients) reporting RVR, were CEf = 18.3% vs. 12.7%; RE = 1.206; 95% CI = 1.059–1.374 ($P = 0.0048$), heterogeneity $Q = 1.116$ and $I^2 = 0.0\%$ ($P = 0.7733$).

Based on the funnel plots (Figure 3) and statistical tests, comparisons of both drugs in all qualified publications yielded low probability of publication bias.

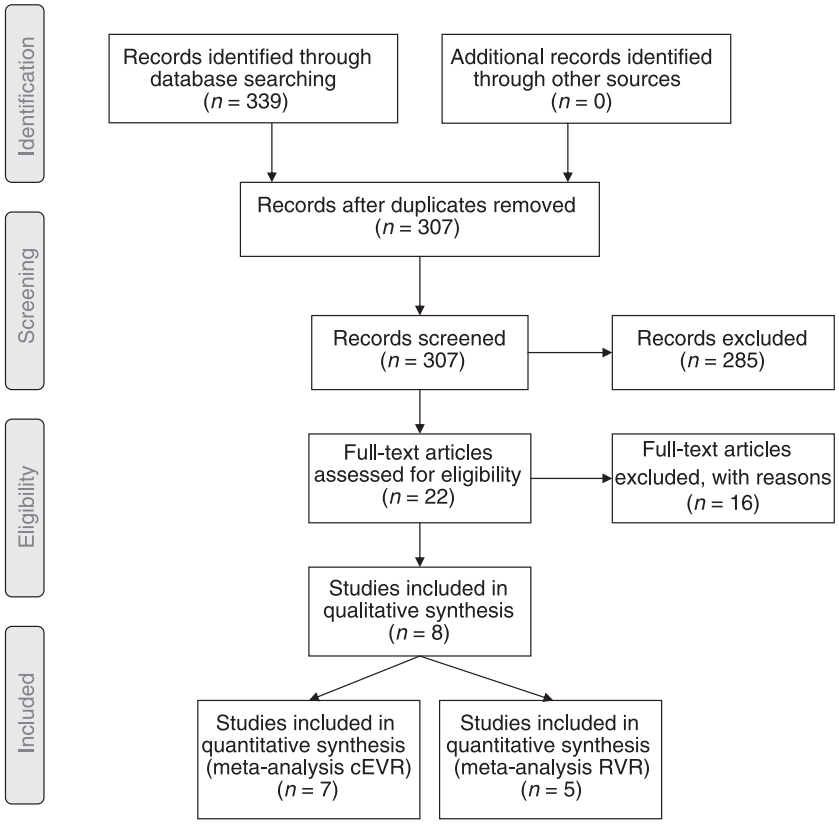


Figure 1 | Study screening flow chart.

Table 1 | Summary of the characteristics of included trials

Study	Year	*n*	Peginterferon α2a (μg/wk)	Peginterferon α2b (μg/kg/wk)	Ribavirin	HCV genotypes	Outcomes reported
A. Studies included in cEVR Analysis							
Ascione*	2010	320	180	1.5	1.0–1.2 g/day	1, 2, 3, 4	cEVR SVR
Berak	2005	237	180	1.0	Weight-based	2, 3 excluded	cEVR
Bruno	2004	22	180	1.0	1.0–1.2 g/day	1, 2, 3	cEVR RVR
McHutchison*	2009	3070	180	1–1.5	0.8–1.4 g/day	1	cEVR RVR SVR
Rumi*	2010	431	180	1.5	0.8–1.2 g/day	1, 2, 3, 4	cEVR RVR SVR
Scotto	2008	143	180	1.5	15 mg/kg/day	1, 2, 3, 4	cEVR SVR
Marcellin*,†	2011	161	180	1.5	0.8–1.2 g/day	1, 2, 3, 4	cEVR RVR
Total *n* = 4384							
B. Studies included in RVR Analysis							
Bruno	2004	22	180	1.0	1.0–1.2 g/day	1, 2, 3	cEVR RVR
Laguno*	2009	182	180	1.5	0.8–1.2 g/day	1, 2, 3, 4	RVR SVR
McHutchison*	2009	3070	180	1-1.5	0.8–1.4 g/day	1	cEVR RVR SVR
Rumi*	2010	431	180	1.5	0.8–1.2 g/day	1, 2, 3, 4	cEVR RVR SVR
Marcellin*,†	2011	161	180	1.5	0.8–1.2 g/day	1, 2, 3, 4	cEVR RVR
Total *n* = 3866							

cEVR, complete early viral response; RVR, rapid viral response; SVR, sustained viral response.

* Studies that report cEVR and EVR of all genotypes and also 1 and 4 independently.

† Triple therapy study of peginterferon, RBV and Telaprevir 2.25 g/day.

Table 2 | Jadad scale to assess RCT quality[20]

Study	Year	Randomised (yes/no)	Appropriate Randomisation method	Double Blinded	Masked	Losses reported	Jadad scale
Ascione*	2010	1	1	0	0	1	3
Berak	2005	1	0	0	0	0	1
Bruno	2004	1	0	0	0	1	2
McHutchison*	2009	1	1	1	1	1	5
Rumi*	2010	1	1	0	0	1	3
Scotto	2008	1	1	0	0	1	3
Marcellin*,†	2011	1	1	0	0	1	3

* Studies that report cEVR and EVR of all genotypes and also 1 and 4 independently.

† Triple therapy study of peginterferon, RBV and Telaprevir 2.25 g/day.

Maximum value, 5 points, indicates highest quality.

DISCUSSION

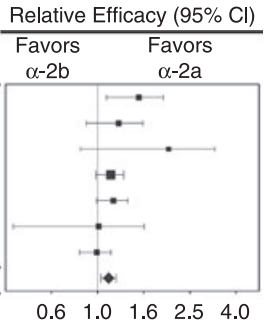
Awad *et al.*,[18] in a previous meta-analysis, showed that pegylated interferon α-2a was associated with a higher SVR than α-2b. Although their conclusion is very useful for clinical practice, as SVR is the ultimate success marker, our objective was to analyse possible differences between these drugs in terms of earlier outcome measures. Our results indicate that peginterferon α-2a might be also superior to α-2b in RVR and cEVR, as shown in individual studies. This knowledge may be useful in the light of present therapeutic and experimental approaches, as RVR and cEVR provide the most relevant information for decision-making. Taking into account the results of Awad *et al.* on SVR, and our own results, the overall efficacy of peginterferon α-2a was 11% or higher than that of peginterferon α-2b when all genotypes were considered, and 20% higher when only data on genotypes 1 and 4 were included.

Hepatitis C virus treatments are evolving and some issues are still the focus of major efforts, such as the possibility of treatment-shortening and some alternatives for achieving success in non responders. As several decisions have to be made during the course of treatment, early outcome measures are necessary to apply guided therapy. In the case of triple therapy, a 4-week treatment regimen with peginterferon and ribavirin, termed the lead-in phase, was developed as a boceprevir strategy to increase SVR and to prevent the development of resistant strains. Because a protease inhibitor is not used during this period, the quantification of HCV RNA at week 4 could be useful in predicting the necessity of triple therapy in patients achieving RVR. It could also be useful in selecting patients showing resistance to interferon plus ribavirin who, for this reason, do not have a chance of cure. Thus, the analysis of RVR during the lead-in phase could allow decisions to be made regarding the management of hepatitis C patients in the triple therapy era.

On the other hand, it has been shown that a decline lower than 1 $\log_{10}$ IU/mL predicts non response, and could be accepted as a stopping rule in previous null-responders, as SVR in these patients is approximately 30%.[25] Consequently, early information may help to prevent futile continuation, avoiding the risk of adverse events and the costs of possibly unsuccessful treatment, and to improve the therapeutic approach to achieve higher SVR rates. The introduction of the first direct-acting medications for HCV (telaprevir and boceprevir) is a major new breakthrough in hepatitis C treatment, and triple therapy of peginterferon and ribavirin with one of these protease inhibitors has shown good results, increasing SVR and reducing relapse in patients infected with genotype 1.[26] Early measure outcomes are of considerable use for these new treatments to help to identify responding patients and to prevent possible resistances due to unnecessary lengthening of drug exposure, because both developed protease inhibitors have been described as prone to resistance.[26, 27] Furthermore, choosing the most appropriate interferon to be combined with the protease inhibitor might impact RVR and success rates. The calculation of this possibility is beyond the scope of this meta-analysis, but is warranted in the near future. HCV usually presents many genetically distinct circulating quasispecies due to its high variability. Drug-resistant variants may be selected by direct-acting antiviral therapy, thus decreasing the numbers of wild-type virus, while the mutated virus gains replication fitness. In this situation, and in view of new possible

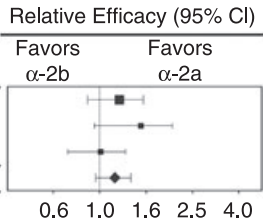
Forest Graph of cEVR results. All HCV genotypes

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Ascione	2010	121	160	104	160	320	1.164	(0.974; 1.391)
Berak	2005	58	101	53	111	212	1.203	(0.911; 1.588)
Bruno	2004	9	10	6	12	22	1.800	(0.977; 3.318)
McHutchison	2009	446	1035	773	2035	3070	1.134	(0.988; 1.303)
Rumi	2010	170	212	151	219	431	1.163	(0.998; 1.356)
Scoto	2008	16	70	18	72	143	0.901	(0.496; 1.639)
Marcellin	2012	70	80	72	81	161	0.984	(0.843; 1.149)
TOTAL		890	1669	1177	2690	4359	1.118	(0.039; 1.203)
Heterogeneity		Qh=	8.959		*P* = 0.176			
Association		QA=	8.909		*P* = 0.003			



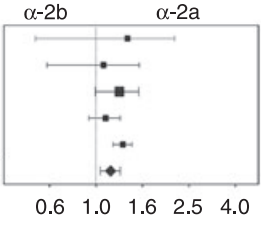
Forest Graph of cEVR results. HCV genotypes 1 and 4

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
McHutchison	2009	466	1035	773	2035	3070	1.185	(0.903; 1.556)
Rumi	2010	60	91	40	87	178	1.434	(0.986; 2.085)
Marcellin	2012	70	80	72	81	161	0.984	(0.743; 1.304)
TOTAL		596	1206	885	2203	3409	1.151	(0.968; 1.369)
Heterogeneity		Qh=	9.802		*P* = 0.007			
Association		QA=	2.520		*P* = 0.112			



Forest Graph of RVR results. All HCV genotypes

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Bruno	2004	7	10	7	12	22	1.200	(0.641; 2.247)
Laguno	2009	27	77	25	72	149	1.010	(0.651; 1.566)
McHutchison	2009	123	1035	195	2035	3070	1.240	(1.002; 1.535)
Rumi	2010	132	212	125	219	431	1.091	(0.934; 1.274)
Marcellin	2012	65	80	55	81	161	1.197	(0.997; 1.437)
TOTAL		354	1414	407	2419	3833	1.151	(1.042; 1.272)
Heterogeneity		Qh=	1.461		*P* = 0.834			
Association		QA=	7.689		*P* = 0.006			



Forest Graph of RVR results. HCV genotypes 1 and 4

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Laguno	2009	8	51	8	39	90	0.315	(1.856; 0.765)
McHutchison	2009	123	1035	195	2035	3070	1.002	(1.345; 1.240)
Rumi	2010	34	91	26	87	178	0.823	(1.898; 1.250)
Marcellin	2012	65	80	55	81	161	0.997	(1.437; 1.197)
TOTAL		230	1257	284	2242	3499	1.206	(1.059; 1.374)
Heterogeneity		Qh=	1.115		*P* = 0.773			
Association		QA=	7.956		*P* = 0.005			

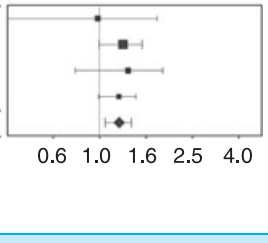


Figure 2 | Forest plots. Analysis of the relative efficacy of peginterferon α2a and α2b in terms of the different outcome measures and according to virus genotype.

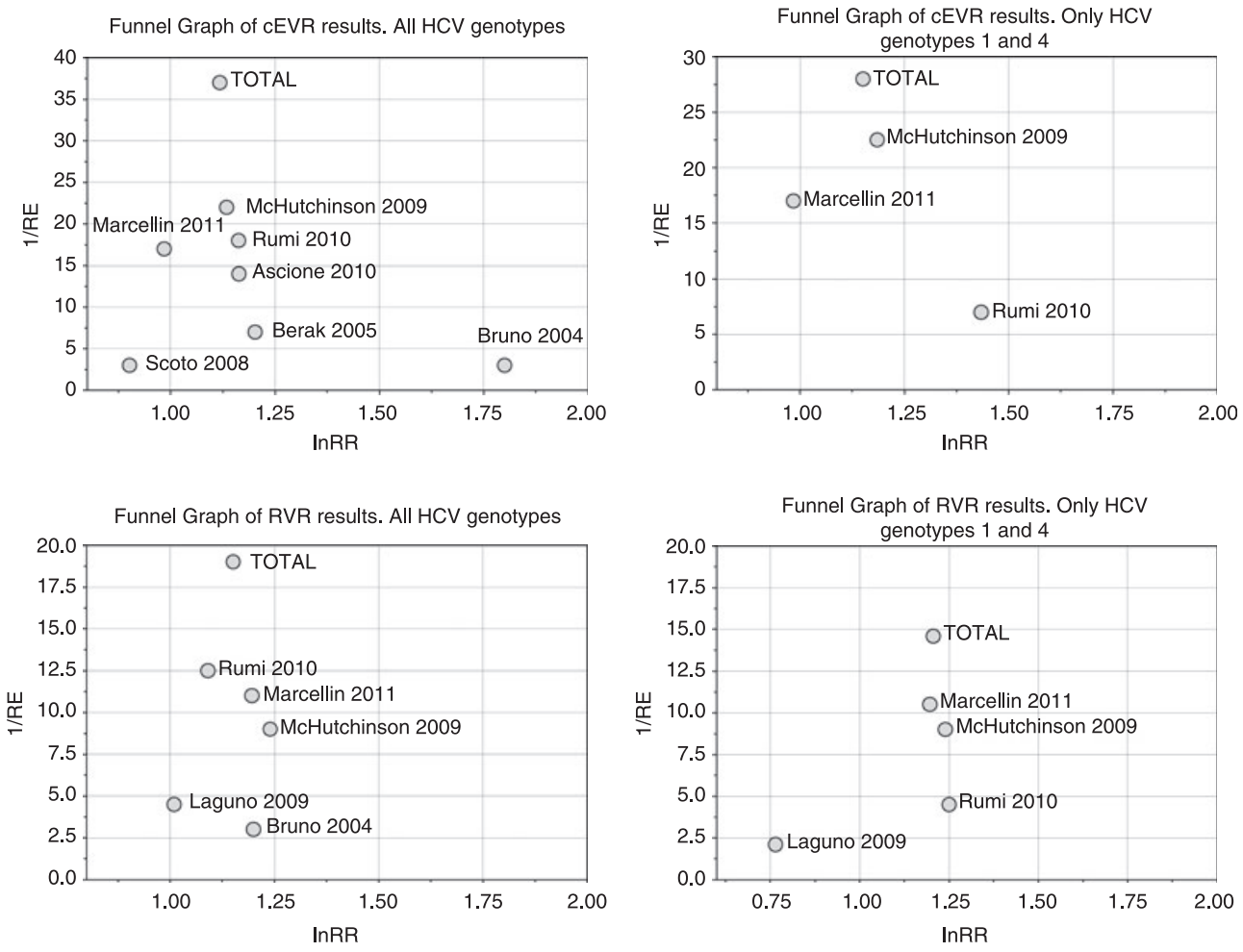


Figure 3 | Funnel graphs. Analysis of publication bias.

direct-acting drug developments, it is relevant to establish useful stopping rules to avoid viral resistance and minimise side effects. Both boceprevir and telaprevir have recent FDA-approved treatment regimens in combination with peginterferon and RBV for genotype 1 HCV[28] that include stopping rules based on early response outcomes: HCV RNA 4 weeks and 12 weeks from initiation of treatment.

Not only possible resistances, but difficulties with treatment compliance in HCV patients,[29] significant side effects and pharmacoeconomic issues of antiviral therapy[30, 31] have led some researchers to explore possible strategies that might shorten treatment periods, using earlier response markers. A study by Cammà *et al.*[32] assessed the cost-effectiveness of five different triple therapy strategies with first generation protease inhibitors compared to dual therapy in the treatment of naïve patients with chronic hepatitis C genotype 1. The analyses suggest that boceprevir-RVR-guided strategy is dominant compared to both boceprevir response-guided therapy and boceprevir IL28B-genotype-guided strategy. Similarly, the telaprevir IL28B-genotype-guided strategy is dominant compared to the telaprevir response-guided therapy.

With respect to the strength of our results, we used extensive searches up to the most recent date possible, and considered the risk of systematic errors (bias). No further studies were identified to be included in this meta-analysis in a search performed until December 2012. Although some authors object to the use of Funnel plots when few studies are included, these graphs are shown to provide as much information as possible. One of the studies included was available only in abstract form,[10] which made full methodological quality assessment impossible. Nevertheless, it fulfilled all the inclusion criteria and contained the desired outcome

measures, and was thus included. Large trials included in this study reported full methodological quality items and dominate the overall estimates of effect, which may overcome the influence of some of the few small-sized trials included that reported incomplete information. To assess the possibility of bias, sensitivity analyses for the studies by Laguno *et al.* and Marcellin *et al.* were performed. These were excluded from the sub-analyses as the former included co-infected patients, and the latter was the only head-to-head study on triple therapy in our analysis. These sensitivity analyses did not reveal any major change in intervention, and there were no relevant inconsistencies among studies, although few trials could be selected with our inclusion criteria and outcomes of interest. Future reviews including new trials could strengthen these results.

These findings may support clinical decisions that could improve SVR rates, as the most appropriate therapy can be selected sooner using early efficacy markers, and also contribute to shortening treatment duration in triple combination therapy. This may have an impact on associated therapy costs, a possibility that could be explored with a pharmacoeconomic analysis.[32]

AUTHORSHIP

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Author contributions: MRG and conceived the study and drafted the paper with JT, RP and RS designed and performed the bibliographical searches; JGS and MD selected the data and collaborated in the statistical analyses with JC and JLC. All authors approved the final version of the manuscript.

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