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

Best Practice/Intervention:	Awad T. et al. (2010) Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology, 51(4):1176-1184.
Date of Review:	February 8, 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:** **Patients with chronic HCV in randomized clinical trials given pefinterferon alpha-2a or peginterferon alfa-2b with or without cointerventions, excluding patients that had undergone liver transplant** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Denmark** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; systematic review of randomized clinical trials to assess the benefits and harms of peginterferon alpha-2a and peginterferon alfa-2b treatments in chronic hepatitis C patients
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Intention-to-treat analysis for SVR shows peginterferon alpha-2a significantly

				increased the number of patients who achieve an SVR (47%) versus peginterferon alfa-2b (41%)
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	8 trials (4,335 participants) were included in the intention-to-treat analysis for sustained virological response
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	All RCT reviewed were collected irrespective of language or publication status from various databases
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 clearly described
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Similar analysis can be made if using the same database and selection criteria
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Hematology*
International guideline or protocol has been established	☒	☐	☐	Review is based on the peer-reviewed published Cochrane Hepato-Biliary Group protocol

The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Easily downloaded 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***	☐	☐	☐	The article is supported by the Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Center for Clinical Intervention Research and Copenhagen University Hospital
Other relevant information: _____	☐	☐	☐	- Evidence suggests peginterferon alpha-2a achieves significantly higher SVR than peginterferon alpha-2b - Future research trials needs to be done to further correlation between achieving SVR and clinical relevant outcome

Peginterferon alpha-2a Is Associated with Higher Sustained Virological Response than Peginterferon alfa-2b in Chronic Hepatitis C: Systematic Review of Randomized Trials

Tahany Awad,[1] Kristian Thorlund,[1] Goran Hauser,[2] Davor Stimac,[2] Mahasen Mabrouk,[3] and Christian Gluud[1]

A combination of weekly pegylated interferon (peginterferon) alpha and daily ribavirin represents the standard of care for the treatment of chronic hepatitis C according to current guidelines. It is not established which of the two licensed products (peginterferon alpha-2a or peginterferon alfa-2b) is most effective. We performed a systematic review of head-to-head randomized trials to assess the benefits and harms of the two treatments. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. Using standardized forms, two reviewers independently extracted data from each eligible trial report. We statistically combined data using a random effects meta-analysis according to the intention-to-treat principle. We identified 12 randomized clinical trials, including 5,008 patients, that compared peginterferon alpha-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin. Overall, peginterferon alpha-2a significantly increased the number of patients who achieved a sustained virological response (SVR) versus peginterferon alfa-2b (47% versus 41%; risk ratio 1.11, 95% confidence interval 1.04-1.19; $P = 0.004$ [eight trials]). Subgroup analyses of risk of bias, viral genotype, and treatment history yielded similar results. The meta-analysis of adverse events leading to treatment discontinuation included 11 trials and revealed no significant differences between the two peginterferons. *Conclusion:* Current evidence suggests that peginterferon alpha-2a is associated with higher SVR than peginterferon alfa-2b. However, the paucity of evidence on adverse events curbs the decision to definitively recommend one peginterferon over the other, because any potential benefit must outweigh the risk of harm. (HEPATOLOGY 2010;51:1176-1184.)

Globally, an estimated 170 million people are chronically infected with hepatitis C virus, and 3 to 4 million persons are infected each year.[1] Analysts estimate the United States prescription market for hepatitis C to be approximately $3 billion annually. A combination of weekly subcutaneous injections of long-acting pegylated interferon (peginterferon) and oral ribavirin represents the current standard of care according to the American Association for the Study of Liver Diseases practice guideline.[2] Currently, there are two licensed products: peginterferon alpha-2a (Pegasys, Hoffmann-La Roche) and peginterferon alfa-2b (PegIntron, Schering-Plough Corporation). Lately, there has been considerable controversy over which treatment options are the most

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OIS, optimum information size; peginterferon, pegylated interferon; RCT, randomized clinical trial; RR, risk ratio; SVR, sustained virological response.

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effective. A recent randomized clinical trial (RCT) published in the *New England Journal of Medicine* concluded that the two treatments are comparable in both benefits and harms.[3] However, findings from a single RCT, even a very large one, are rarely definitive, and caution should be taken to ensure reproducibility of its findings.[4-9] Systematic reviews and meta-analysis including all available trials are considered the highest level of evidence, and provide valuable information on the quality and strength of the available evidence.[10] We therefore conducted a Cochrane systematic review to identify, assess, and collectively analyze all RCTs that would add to the body of evidence and strengthen inferences about which form of peginterferon may work best.

Materials and Methods

The present systematic review is based on our peer-reviewed published Cochrane Hepato-Biliary Group protocol.[11]

Eligibility Criteria. This review includes RCTs, irrespective of language or publication status, comparing peginterferon alpha-2a with peginterferon alfa-2b given with or without cointerventions (such as ribavirin) in patients with chronic hepatitis C. We excluded RCTs if they included patients that had undergone liver transplantation.

Outcomes. The prespecified primary outcomes were sustained virological response (SVR), liver-related morbidity plus all-cause mortality, and adverse events leading to treatment discontinuation. SVR was defined as the number of patients with undetectable hepatitis C virus RNA in serum by sensitive test 6 months after the end of treatment.

Data Sources and Searches. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. We identified further trials by searching conference abstracts, journals, and gray literature. We used the key words *hepatitis C*, *peginterferon*, *pegylated interferon*, *viraferonpeg*, *pegintron*, and *pegasys* either as MeSH terms or as free-text words.

Study Selection and Data Collection. Two authors independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data using a standardized data collection form to record study design and methodological characteristics, patient characteristics, interventions, outcomes, and missing outcome data. Authors of included trials were contacted for additional information not described in the published reports.

Methodological Quality Assessment. Methodological quality and hence risk of bias was defined as the confidence that the design and the report of the RCT would restrict bias in the comparison of the intervention.[12] The assessment was based on published reports and information provided by the authors of included trials. Following the implications of empirical evidence,[12-14] the methodological quality of the trials was assessed based on sequence generation allocation concealment, blinding of outcome assessors, incomplete outcome data (lost to follow-up and adherence to intention-to-treat analysis), and early stopping for benefit.

Data Synthesis and Analysis. The analyses were performed using Review Manager 5.0 and Trial Sequential Analysis version 0.8. Dichotomous data were expressed as the risk ratio (RR) with 95% confidence interval (CI). Furthermore, the number needed to treat was derived from the RR in meta-analyses where the 95% CI (or the RR) did not include zero. Heterogeneity was explored using a chi-square test, and the quantity of heterogeneity was measured using the I^2 statistic.[15] Sources of heterogeneity were assessed with subgroup analysis and meta-regression whenever possible. Subgroup analyses were performed only when data from at least two trials were available for each subgroup. Meta-regression was performed only for meta-analyses including more than 10 trials. Suitable sensitivity analysis was identified during the review process. When patients were lost to follow-up, data were analyzed according to the intention-to-treat principle. Intention-to-treat analysis was performed assuming poor outcome in both groups, where dropouts were considered failures and the total number of patients was used as the denominator. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[16] to present the summary of findings for the patient important outcomes.

Assessment of Reliability and Meta-analysis Sample Size Requirements. To assess the reliability of pooled inferences from our meta-analysis on SVR, we calculated the optimum information size (OIS)—that is, the required meta-analysis sample size—to detect a 10% relative risk reduction in SVR, assuming an average event rate of 50% in the two treatment arms, assuming that 30% of the variation in the meta-analysis would be explained by variation across trials, and using statistical error levels of alpha = 5% and beta = 10% (90% power). Meta-analyses conducted before surpassing their OIS are analogous to interim analyses in single RCTs, and thus necessitate adjustment of the threshold for statistical significance to maintain the predetermined maximum risk of obtaining a false positive results (set to alpha 5% in our analysis). We therefore substituted the conventional 5% threshold for statistical significance with those of Lan-DeMets alpha-spending monitoring boundaries.[8,17-19]

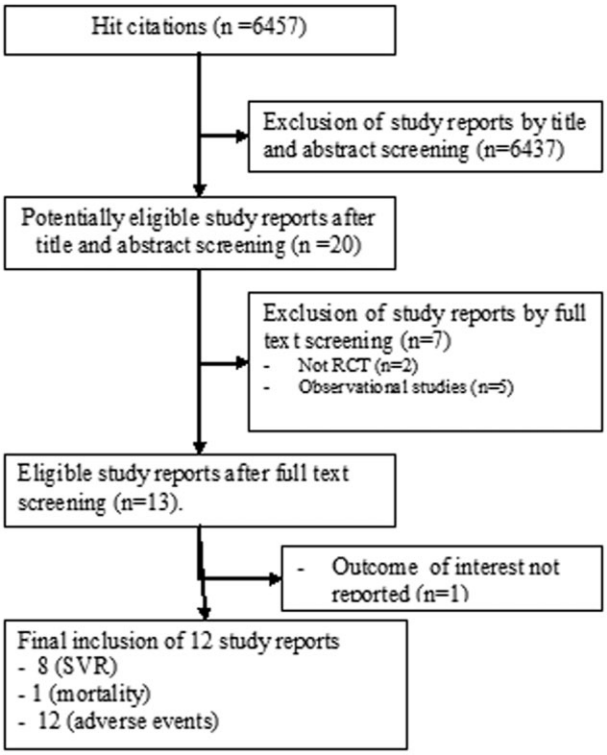

Fig. 1. Study screening flow chart.

Results

Study Characteristics. Figure 1 shows the results of the study screening. Twelve trials, including a total number of 5,008 participants,[3,20-30] that met our inclusion criteria[31] were retrieved. All trials compared peginterferon alpha-2a (180 μg/week) versus peginterferon alfa-2b (1-1.5 μg/kg/week). All trials administered ribavirin as a cointervention to both peginterferon arms. The dose of ribavirin was weight-based, ranging from 800 to 1,400 mg. The hepatitis C genotype of the included patients varied among trials. One trial included patients with history of previous hepatitis C treatment.[26] One trial included patients with human immunodeficiency virus patients.[24] Table 1 presents the patient and intervention characteristics. Table 2 presents the methodological quality of eligible randomized trial.

Effects of Interventions. The meta-analysis using intention-to-treat analysis for SVR included eight trials (4,335 participants).[3,23-26,28-30] Overall, peginterferon alpha-2a significantly increased the number of patients who achieved an SVR (47%) versus peginterferon alfa-2b (41%) (RR 1.11, 95% CI 1.04-1.19; $P = 0.004$). The number needed to treat was 25 patients (95% CI 14-100). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.58, and the heterogeneity was $I^2 = 0\%$ (Fig. 2).

Most subgroup analyses revealed no significant interactions. Data from six trials[3,24-26,29,30] for genotype 1 and 4 yielded an RR in favor of peginterferon alpha-2a (RR 1.21, 95% CI 1.03-1.42). Using relative risk as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.21, and the heterogeneity was $I^2 = 30\%$. Data from five trials[23-26,30] for genotype 2 and 3 yielded an RR in favor of peginterferon alpha-2a (RR 1.11, 95% CI 1.02-1.22). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.89, and the heterogeneity was $I^2 = 0\%$.

Sensitivity analyses revealed no change in the significance of effects, and there was no significant change of magnitude of treatment effects. A sensitivity analysis including only trials with adequate randomization and allocation concealment did not change the pooled estimate. Additionally, excluding the trial that included patients with human immunodeficiency virus and the trial with nonresponder patients did not change the pooled estimate.

To assess the reliability of pooled inferences from our meta-analysis on SVR, we calculated the OIS required to detect a 10% relative risk reduction in SVR to be 5,990 patients. Statistical significance assessed with Lan-DeMets alpha-spending monitoring boundaries are presented in Fig. 3. Based on the adjusted threshold for statistical significance the meta-analysis on SVR was still significant in favor to peginterferon alpha-2a.

Adverse events leading to treatment discontinuation were reported in 11 trials.[3,20-22,24-30] Data from these trials yielded an RR of 0.79 (95% CI 0.51-1.23). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.42, and the heterogeneity was $I^2 = 2\%$ (Fig. 4). Furthermore, the included trials reported on numerous adverse events that did not lead to treatment discontinuation. Adverse events included hematological changes (neutropenia, thrombocytopenia, and anemia), psychological changes (depression), and other systemic events (fatigue, headache, insomnia, fever, nausea, and dyspnea). None of the included trials reported on any patients with liver-related morbidity.

Only one trial reported on all-cause mortality.[3] Seven patients died during the treatment period, and five died during or after the follow-up period. Two of these deaths were due to a suicide 6 months after the end of treatment with peginterferon alfa-2b and a myocardial infarction during treatment with peginterferon alfa-2a.

Table 3 presents the GRADE evidence profile regarding SVR and adverse events leading to treatment discontinuation.

Discussion

In this systematic review, we have summarized the available evidence from RCTs comparing peginterferon

Table 1. Characteristics of the Included Trials

Study	Peginterferon	Ribavirin	Ribavirin Dose Modification	Baseline Treatment History	HCV Genotype	Outcome Reported
Ascione (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	1,000-1,200 mg/day†	200 mg‡	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Berak (2005)	alpha-2a, 180 μg/week alfa-2b, 1.0 μg/kg/ week for 12 weeks	Weight-based	NR	NR	Non 2/3	Adverse events
Bruno (2004)	alpha-2a, 180 μg/week alfa-2b, 1.0 μg/kg/ week for 12 weeks	1,000-1,200 mg/day†	NR	Treatment-naïve	1, 2, 3	Adverse events
DiBisceglie (2007)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 12 weeks	1,000-1,200 mg/day†	NR§	Treatment-naïve	1	Adverse events
Kolakowska (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24 weeks	Weight-based	NR	Treatment-naïve	3	SVR, adverse events
Laguno (2009)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 48 weeks	800-1,200 mg/day¶	NR	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
McHutchison (2009)	alpha-2a, 180 μg/week alfa-2b, 1-1.5 μg/kg/ week for 24-48 weeks*	800-1,400 mg/day$	200-600 mg**	Treatment-naïve	1	SVR, adverse events
Rumi (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	800-1,200 mg/day††	200 mg#	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Scotto (2008)	alpha-2a, 180 μg/week alfa-2b 1.5 μg/kg/ week for 24-48 weeks*	15 mg/kg/day	4.6 mg/kg/day	Nonresponders	1, 2, 3, 4	SVR, adverse events
Silva (2006)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 8 weeks	13 mg/kg/day	None allowed	Treatment-naïve	1	Adverse events
Sinha (2004)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	1,000-1,200 mg/day	NR	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Yenice (2006)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	800-1,200 mg/day§§	200-600 mg¶¶	Treatment-naïve	1	SVR, adverse events

*Patients affected by genotypes 1 or 4 received 48 weeks of treatment, while those affected by genotypes 2 or 3 were treated for 24 weeks.

$Peginterferon alfa-2b arm: 40-65 kg, 800 mg/day; >65-85 kg, 1,000 mg/day; >85-105 kg, 1,200 mg/day; and >105-125 kg, 1,400 mg/day. Peginterferon alpha-2a arm: <75 kg, 1,000 mg/day; ≥75 kg, 1,200 mg/day.

†1,000 mg/day in patients <75 kg, 1,200 mg/day in patients ≥75 kg.

‡Reduced in 200-mg decrements if the hemoglobin level decreased to <100 g/L or ≥30 g/L, or in the event of a severe cough or intolerable itching. Ribavirin was discontinued if the hemoglobin level decreased to <85 g/L.

§The reduction dose was not stated; however, the same dose reduction was applied for both arms.

¶800 mg for body weight <60 kg; 1,000 mg for 60-75 kg; 1,200 mg for >75 kg.

**For the peginterferon alfa-2b arm, the dose reduction occurred in two steps. The first step was a reduction of either 200 mg (in patients receiving 800-1,200 mg/day ribavirin) or 400 mg (in patients receiving 1,400 mg/day). The second step was reduction by another 200 mg, if required for resolution of the adverse event. For the peginterferon alpha-2a arm, the dose reduction consisted of a reduction to 600 mg/day. For all patients, ribavirin dose reduction was required if the hemoglobin level was <10 g/dL. Treatment with both drugs was permanently discontinued if the level was <8.5 g/dL.

††For the peginterferon alpha-2a arm, genotypes 1 and 4 were given 1,000 mg/day for <75 kg and 1,200 mg/day for ≥75 kg; genotypes 2 and 3 were given 800 mg/day. For the peginterferon alfa-2b arm, the doses were 800 mg/day for <65 kg, 1,000 mg for 65-85 kg, and 1,200 mg for ≥85 kg.

‡‡Ribavirin dose was reduced by 200 mg/day in patients with a hemoglobin level <10 g/dL, whereas it was discontinued in patients with <8.5 g/dL hemoglobin.
Abbreviation: HCV, hepatitis C virus; NR, not reported; SVR, sustained viral response.

§§40-64 kg, 800 mg; 65-85 kg, 1,000 mg; >85 kg, 1,200 mg.

¶¶Ribavirin dose was reduced to 600 mg in patients with a hemoglobin level <10 g/dL who had no cardiac problems. The same dose was maintained until the end of treatment. Ribavirin treatment was discontinued when the hemoglobin level was <8.5 mg/dL.

alpha-2a with peginterferon alfa-2b, both given in combination with weight-based ribavirin. Our results suggest that the combination of peginterferon alpha-2a and weight-based ribavirin may achieve significantly higher SVR than the combination of peginterferon alfa-2b and weight-based ribavirin. Only one trial reported mortality.[3] None of the included trials reported on liver-related morbidity. Our results also suggest that the two peginter-

Table 2. Methodological Quality of Eligible Trials

Trial	Concealment of Allocation	Outcome Assessors Blinded	Loss to Follow-up	Adherence to Intention-to-Treat Principle	Stopping Early for Benefits
Ascione (2008)	Yes	Yes	0	Yes	No
Berak (2005)	Unclear	Unclear	6	Yes	No
Bruno (2004)	Yes	Unclear	0	Yes	No
DiBisceglie (2007)	Yes	Unclear	45	Yes	No
Kolakowska (2008)	Unclear	Unclear	0	Unclear	No
Laguno (2009)	Yes	Unclear	34	Yes	No
McHutchison (2009)	Yes	Unclear	653	Yes	No
Rumi (2008)	Yes	Unclear	119	Yes	No
Scotto (2008)	Yes	Unclear	18	Yes	No
Silva (2006)	Yes	Yes	6	No	No
Sinha (2004)	Yes	Unclear	1	Yes	No
Yenice (2006)	Unclear	Unclear	6	Unclear	No

ferons may be comparable with regard to adverse events leading to treatment discontinuation. However, evidence on liver-related morbidity or mortality and adverse events is sparse, and the meta-analysis on adverse events is likely to be underpowered to detect any difference.

The GRADE findings in Table 3 show that in general, we can have high confidence in the current evidence on treatment benefits (measured as SVR), whereas we can only have low confidence in the current evidence on harms (measured as adverse events leading to discontinuation). For both outcomes, there were no serious limitations in the study design of the included trials. Information on the methodological quality was incomplete in a few small-sized trials. However, our sensitivity analyses did not reveal any important change of intervention effects. In our study, the trials that adequately reported methodological quality items are large trials, and dominate the pooled estimates of effect. Therefore, it is unlikely that pooled estimates are biased. In the meta-analyses for SVR, there were no serious inconsistencies across trials and the meta-analyses had adequate precision adjudicated by crossing of the adjusted threshold for statistical significance (the Lan-DeMets monitoring boundaries). Only a comparison of the largest trial[3] with the second and third largest trials[25,30] yielded moderate discrepancy. The latter two were both sufficiently statistically powered to detect a difference between the two peginterferons, and unlike the largest trial, which was funded by the manufacturer of peginterferon alfa-2b, these two trials were not funded by either of the two manufacturers. Because the meta-analysis for SVR only included eight trials, we did not perform a funnel plot to explore publication bias; however, because this meta-analysis included a seemingly reasonable mix of small and large trials yielding fairly consistent results, publication bias presented little concern. Nonetheless, we have some concerns with regard to indirectness. In the identified trials, virological response was the predominant measure of benefit. Many of the trials measured SVR, which is currently the commonly used surrogate outcome measure of benefit. Recent large cohort studies show correlation between the presence of viremia and mortality.[31,32] However, it is important to remember that SVR (and early virological response and end-of-treatment virological re-

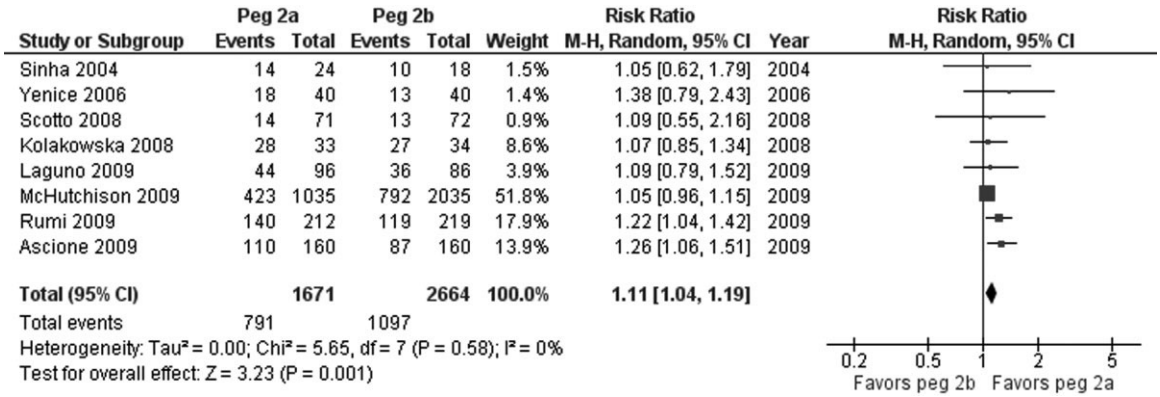

Fig. 2. Forest plot of comparison: Peginterferon alpha-2a versus peginterferon alfa-2b, outcome: Sustained virological response.

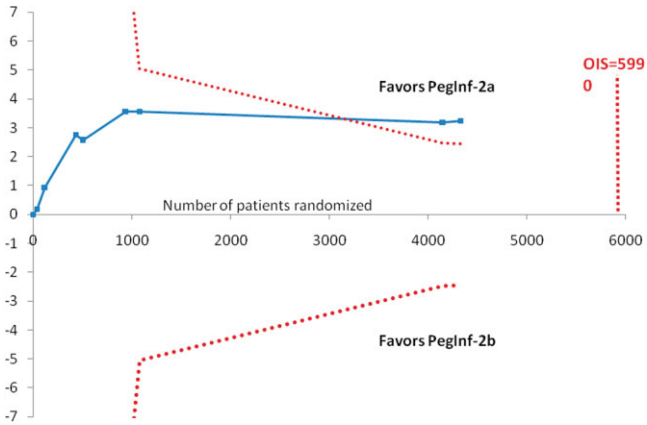

Fig. 3. Lan-DeMets statistical monitoring boundaries for assessing statistical significance. The solid blue curve presents the cumulative meta-analysis test-score and the inward sloping red dotted curves present the adjusted threshold for statistical significance—the two-sided LanDeMets monitoring boundaries. Test scores above the upper monitoring boundaries are statistically significant in favor of peginterferon alpha-2a (at an alpha = 5% level).

sponse) is still only a putative (that is, nonvalidated) surrogate outcome.[33] Because RCTs need to inform clinical practice, clinical outcomes such as the risk of liver failure, hepatocellular carcinoma, and mortality would be of greater interest to patients and clinicians. Such measures nevertheless require a follow-up of at least 5 years. Currently, no RCTs comparing the two peginterferons are of such longevity. In the meta-analysis on adverse events, there were serious discrepancies across trials. The proportions of observed adverse events differed greatly across the trials, and the direction of effect was also heterogeneous. It is noteworthy that the IDEAL trial[3] included three intervention arms: one for peginterferon alpha-2a and two for peginterferon alfa-2b. The two peginterferon alfa-2b arms consisted of a regular 1.5 μg/kg/week dosage and a low 1.0 μg/kg/week dosage. The regular dosage arm yielded a similar proportion of adverse events as the peginterferon alpha-2a arm, whereas the low-dose peginterferon alfa-2b group yielded a lower proportion of adverse events. Including or excluding the low-dose peginterferon alfa-2b arm from the meta-analysis had no visible impact on the estimated effect. Furthermore, the meta-analysis on adverse events had low precision. A post hoc OIS calculation that was geared to detect a minimally important difference of 10% relative risk reduction, based on the assumption of average population risk rate of 10%, and employed a 5% maximum type I error and 80% power, suggested that a minimum of 27,000 patients would need to be randomized for a conclusive adverse events meta-analysis. The current number of patients in the adverse events meta-analysis is approximately 5,000 (less than 20% of what is required).

There are some concerns regarding the nonstandardization of the ribavirin dose given across trials. The weight-based dose of ribavirin ranged from 800 to 1,400 mg. However, the weight cutoff varied among trials as well as within the same trial. In the largest included trial,[3] patients weiging 40-65 kg received a lower dose of ribavirin (800 mg) in the peginterferon alfa-2b arm compared with a higher dose of ribavirin (1,000 mg) in the peginterferon alpha-2a arm. However, patients in the peginterferon alfa-2b arm achieved higher SVR compared with patients in the peginterferon alpha-2a arm (46% versus 43%). Also, patients weighing more than 105 kg received a higher dose of ribavirin in the peginterferon alfa-2b arm (1,400 mg) compared with a lower dose of ribavirin (1,200 mg) in the peginterferon alpha 2a arm. Regardless, patients in the peginterferon alfa-2b arm achieved higher

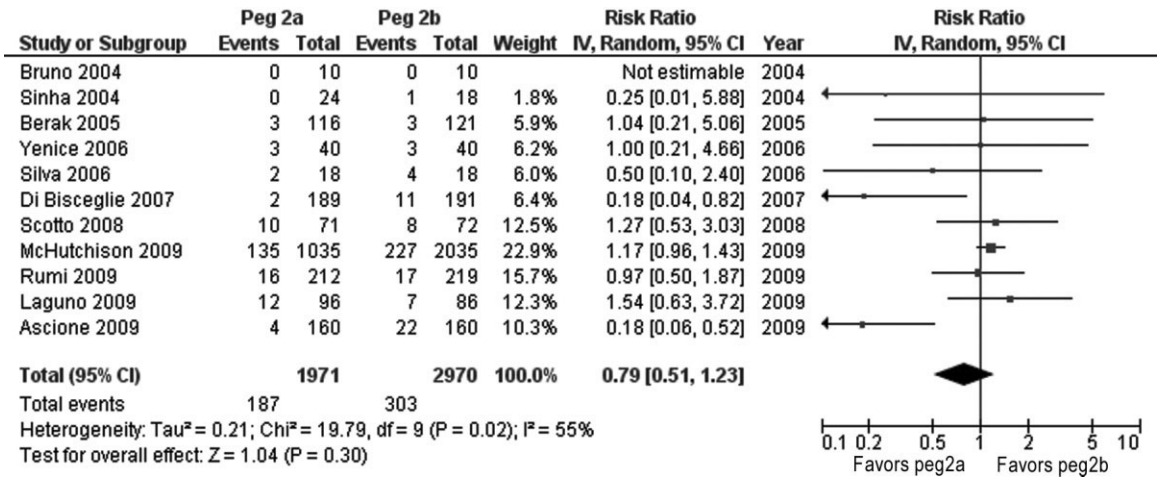

Fig. 4. Forest plot of comparison: Peginterferon alfa-2a versus peginterferon alfa-2b, outcome: Adverse events leading to treatment discontinuation.

Table 3. Summary of Findings: Peginterferon alpha-2a versus Peginterferon alfa-2b for Chronic Hepatitis C

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)†	Comments
	Assumed Risk: Peginterferon alfa-2b	Corresponding Risk: Peginterferon alpha-2a				
SVR	Medium risk population		RR1.1 (1.03-1.18)	4,335 (8)	⊕⊕⊕⊕	
	481 per 1,000	529 per 1,000 (495-568)			High‡	
Adverse events	Medium risk population		RR0.8 (0.51-1.26)	4,621 (10)	⊕⊕⊖⊖	
leading to treatment discontinuation	75 per 1,000	60 per 1,000 (38-94)			Low§,¶,#	

Patient or population: chronic hepatitis C. Intervention: peginterferon alpha-2a. Comparison: **p**eginterferon alfa-2b.

*The basis for the assumed risk (the median control group risk across studies) is provided in the other footnotes in this table. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†GRADE Working Group grades of evidence: High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: We are very uncertain about the estimate.

‡Many of the trials measured SVR, which is currently recognized as the best patient surrogate outcome measure of benefit. However, it is important to remember that SVRs are still only invalidated surrogate outcomes and thus do not necessarily predict patient important outcomes such as liver failure and hepatocellular carcinoma.

§The proportions of observed adverse events differ substantially across the trials, and the direction of effect is heterogeneous. However, because the event rate is still relatively low across all trials, all of the included trials may be subject to considerable random error, thus explaining the apparent heterogeneity in direction of estimates.

¶The Ideal trial includes three groups: one for peginterferon alpha-2a and two for peginterferon alfa-2b. The two peginterferon alfa-2b arms consist of a regular 1.5 dose and a low 1.0 dose. The regular-dose group yields similar proportion of adverse as the peginterferon alpha-2a group, whereas the low-dose peginterferon alfa-2b group yields a lower proportion of adverse events. Including/excluding the low-dose group from the meta-analysis had no visible impact on the pooled effect.

#Post hoc optimal information size calculations based on 5% type I error, 80% power, a minimally important difference of 10%, and an average risk rate of 10% suggest that a minimum of 27,000 patients need to be randomized for a conclusive adverse events meta-analysis. The current number of patients is approximately 5,000.

SVR compared with patients in the peginterferon alpha-2a arm (42% versus 39%). It is also interesting that in the same trial, patients who developed anemia and thus required ribavirin dose reduction achieved a higher SVR than patients who did not require the ribavirin dose to be reduced. Accordingly, we do not think that the varying doses of ribavirin have major confounding influence on our observations regarding type of peginterferon. More research needs to be performed to explore the optimal ribavirin dose. Ribavirin dose reduction due to adverse events was only reported in five trials.[3,25,26,29,30] Four of these trials applied the same dose reduction in both arms.[25,26,29,30] Only one trial applied different ribavirin dose reduction for two arms.[3] Excluding this trial from our meta-analysis for SVR did not change our estimate.

The strengths of this Cochrane Hepato-Biliary Group systematic review are that it is built on a peer-reviewed published protocol, used extensive searches until recently, considers risks of systematic errors (bias), and considers risks of random errors (chance) by adjusting the threshold for statistical significance according to the information and strength of evidence in the cumulative meta-analysis. A possible limitation is the unavailability of full reports of all included trials. Two of the eight included trials in the meta-analysis for SVR are only available as abstracts. However, we were able to successfully retrieve the necessary data for one of the two abstracts via e-mail correspondence with the authors,[28] and thus, the bias risk assessment of the included trial was performed to a satisfactory extent. Our sensitivity analysis did not show any important changes. In our study, the trials that were published as a full paper are large, and dominated the pooled estimates of effects. Moreover, empirical evidence suggests that trials that fail to refute the null hypothesis have lower odds of being published, especially those not funded by the industry.[34-40] Thus, many of the included abstracts may have a low probability of being published. In fact, including these abstracts in our systematic review may likely be a strength rather than a limitation. By including abstracts, we are looking at the complete available body of evidence. By excluding abstracts, we would only be looking at a subset defined through the biased publication mechanisms of the present day, which would increase the likelihood of publication bias considerably. Selective outcome reporting was difficult to assess in this review. Most of the included trials were not adequately registered or had their protocols publicly available prior to trial completion. Hopefully, the initiation of the World Health Organization International Clinical Trials Registry Platform will facilitate such assessments for future trials.[41,42] Another limitation in this review was insufficient reporting. Investigators of future trials are therefore well advised to adhere to the Consolidated Standards for Reporting of Trials in order to improve the quality of trial reports.[43]

These potential limitations and concerns may lower our confidence in the estimates of intervention effect. However, in our meta-analysis for SVR there is no apparent heterogeneity ($I^2 = 0\%$), and the direction of the treatment effect is the same across all included trials. Fur-

ther research is unlikely to change our confidence in the estimate of the effect. It is a common misconception that large RCTs are generally more reliable than meta-analyses. The reason this misconception has prevailed is due to a number of highly cited papers that compared high-quality large trials with collections of low-quality small trials (an unfair comparison). In empirical studies where high-quality large trials are compared with a collection of high-quality small trials, the results from the two are typically nondiscrepant. In the case of the IDEAL trial,[3] the results still show an effect—albeit small—in favor of peginterferon alpha-2a. There are many examples of large trials that underestimate the treatment effect simply by chance.

Current evidence suggests that peginterferon alpha-2a is significantly superior to peginterferon alfa-2b regarding benefits (SVR, which is clearance of the virus from the blood). However, there is insufficient evidence to detect any differences regarding harms (mortality and adverse events). Future trials must further the correlation between achieving SVR and clinically relevant outcomes such as risk of cirrhosis, hepatocellular carcinoma, and mortality.

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