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

Best Practice/Intervention:	Kieran J. et al. (2013) The relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1. *Clinical Infectious Diseases*, 56(2):228-235.
Date of Review:	February 15, 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: HCV genotype 1 patient treated with boceprevir or telaprevir

Setting: Health care setting/Clinic ☒   Home ☐   Other: _____

Country of Origin: Ireland _____

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 to examine the relative difference in efficacy between boceprevir and telaprevir as HCV genotype 1 treatment.
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	10 studies included in the analysis

Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Studies searched from online 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?	☒	☐	☐	Clear methodology
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	Boceprevir and telaprevir may not be easily available 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	☒	☐	☐	*Clinical Infectious Diseases*
International guideline or protocol has been established	☒	☐	☐	Study selection followed PRISMA guidelines
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Free to download from http://cid.oxfordjournals.org/
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**	☐	☒	☐	not funded
Other relevant information: _____	☐	☐	☐	- No significant difference in treatment outcomes between 2 agents in the overall treatment-naive or treatment-experienced

				populations
				- In treatment-experience patients, telaprevir has greater relative efficacy

The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of Hepatitis C Virus Genotype 1

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Background. The licensing of direct-acting antivirals heralds a new era in the treatment of hepatitis C virus (HCV) genotype 1. We undertook a mixed treatment comparison to examine the relative efficacy among current treatments for HCV.

Methods. A systematic literature review identified relevant studies. Meta-analyses were planned in treatment-naive and treatment-experienced patients. Study arms that evaluated telaprevir or boceprevir for unlicensed durations or without both pegylated interferon and ribavirin at standard doses were excluded. A Bayesian mixed treatment comparison model was fitted for each patient population.

Results. Four hundred ninety-nine studies were identified. Ten met inclusion criteria. In the subgroup of prior treatment "relapsers," telaprevir had greater relative efficacy than boceprevir (odds ratio [OR], 2.61 [95% confidence interval {CI}, 1.24–5.52]). There were no statistically significant differences detected in relative efficacy for other patient categories. Treatment-naive patients: boceprevir vs standard of care (n = 1417) (OR, 3.06 [95% CI, 2.43–3.87]); telaprevir vs standard of care (n = 1309) (OR, 3.24 [95% CI, 2.56–4.10]); telaprevir vs boceprevir (OR, 1.06 [95% CI, 0.75–1.47]). Total treatment-experienced population: boceprevir vs standard of care (n = 604) (OR, 6.53 [95% CI, 4.20–10.32]); telaprevir vs standard of care (n = 891) (OR, 8.32 [5.69–12.36]); telaprevir vs boceprevir (OR, 1.27 [95% CI, .71–2.30]).

Conclusions. Telaprevir had greater relative efficacy than boceprevir in patients who had previously relapsed. There was insufficient evidence to detect a difference in treatment outcomes between the 2 agents in the overall population. It was not possible to determine relative efficacy for subgroups such as patients with cirrhosis owing to small numbers.

Keywords. Bayesian; meta-analysis; HCV protease inhibitors; Ireland; hepatitis C.

Chronic hepatitis C virus (HCV) infection is a global health burden of major concern. The World Health Organization (WHO) estimates that 130–170 million people worldwide are chronically infected with HCV and that >350 000 people die of HCV-related disease every year [1]. There are 6 different genotypes of HCV, with genotypes 1 and 3 being the most frequently encountered in Europe and the United States [2, 3]. Because of the morbidity associated with chronic HCV, the strategy in many healthcare systems is to treat the infection before patients reach the later stages of liver disease [4, 5]. Dual therapy with pegylated interferon plus ribavirin (peg-IFN/RBV) given for 48 weeks has been regarded as the standard of care for treating HCV genotype 1 infection for the past decade [4, 5]. This has resulted in successful treatment outcomes, known as sustained virologic response (SVR), in 40%–50% of treated individuals with genotype 1 infection [6–8]. The licensing of 2 new HCV

protease inhibitors, telaprevir and boceprevir, heralds a new era in the treatment of HCV genotype 1 infection [9]. The addition of these agents to the standard-of-care regimen of peg-IFN/RBV results in a significant increase in SVR rates in patients with genotype 1 infection and allows a proportion to be treated for a shorter duration [10, 11–19]. It is likely that this will lower the threshold for treating substantial numbers of patients with HCV infection. As yet, there are no head-to-head comparative trials to identify whether there are differences in efficacy between the protease inhibitors. Network meta-analysis, or mixed treatment comparison, allows calculation of the relative efficacy of treatments in the absence of head-to-head evidence. This is an extension of standard meta-analysis that is used to combine studies looking at a single intervention.

A Bayesian approach is often adopted because it is well suited to the complex evidence structures that arise [20]. Bayesian hierarchical models simultaneously estimate the relative efficacy between treatments that have not been directly compared, and provide the most flexible approach to indirect comparison modeling. The technique was first introduced by Lu and Ades in 2004 [21, 22], and has since become a standard tool in such applications where multiple treatments for a given condition exist [23]. The outcome of a Bayesian analysis is a posterior probability distribution for each parameter of interest. These can be summarized by the mean and a credible interval to capture the uncertainty surrounding the estimate.

We undertook a mixed treatment comparison using this methodology to determine the relative differences in efficacy between boceprevir and telaprevir when used as a third agent in HCV genotype 1 treatment.

METHODS

Systematic Review

A review protocol was developed along with prespecified inclusion criteria using a PICOS structure [24] (Table 1). Medline/PubMed, Embase, The Cochrane Library, and Science Citation Index were searched on 1 November 2011 and the searches were re-run on 3 September 2012. In an effort to reduce the effect of publication bias and to include "gray literature" (ie, research that has not been published as journal articles), a hand-search of conference abstracts from the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) conferences in 2010, 2011, and 2012 was performed. Details of the search strategy can be found in the Supplementary Appendix. The first decision for inclusion was made by 2 reviewers (J. K. and S. S.) on the basis of title and abstract. For studies that appeared to meet the inclusion criteria, the full text was sourced and assessed. Study selection followed PRISMA (Preferred Reporting Items for Systematic Reviews

Table 1. Summary of Inclusion and Exclusion Criteria for the Meta-analysis

Population	Studies of patients aged >18 y chronically infected with HCV genotype 1
Subpopulation	1. Patients with chronic HCV genotype 1 infection who were treatment naive 2. Patients with chronic HCV genotype 1 infection who were treatment experienced
Intervention	Studies where patients were treated with pegylated interferon and ribavirin in combination with either telaprevir or boceprevir. Study arms which evaluated telaprevir or boceprevir for unlicensed durations or without both pegylated interferon and ribavirin at standard doses were excluded.
Outcomes	Rates of sustained viral response in patients receiving pegylated interferon and ribavirin in combination with either telaprevir or boceprevir
Study design	Randomized controlled trials of human subjects that have undergone peer review either for journal publication or for abstract presentation at a major hepatology scientific conference.
Language	No language limits
Subgroups considered	1. Patients with chronic HCV genotype 1 infection who were treatment naive and had black ethnicity 2. Patients with chronic HCV genotype 1 infection who were treatment experienced and had a prior treatment response classified as "relapse"

Abbreviation: HCV, hepatitis C virus.

and Meta-Analyses) guidelines, which consist of a 27-point checklist and a 4-phase flow diagram [24, 25] (Figure 1). Quality of the included studies was assessed using the Cochrane Collaboration "risk of bias" tool [26] (Figure 2). A sensitivity analysis was performed, where the trials of lesser quality were removed and the analysis was re-run.

Meta-analyses were planned in 2 patient populations: (1) patients with chronic HCV genotype 1 infection who were treatment-naive and (2) patients with chronic HCV genotype 1 infection who were treatment-experienced. As interleukin 28B (IL-28B) or other host-related markers of interferon responsiveness were not recorded routinely in the clinical trials, 2 subgroup analyses of the populations studied were planned as surrogate markers for interferon responsiveness. In the treatment-naive group, there was a prespecified subgroup analysis of patients with black ethnicity. Prior treatment response is likely to be the most important predictor of future treatment response in treatment-experienced patients [27]. Therefore, we did a prespecified subgroup analysis of prior treatment "relapsers" vs those whose prior treatment response was otherwise classified. We classified patients in this way due to inconsistencies in the definitions of prior partial and null
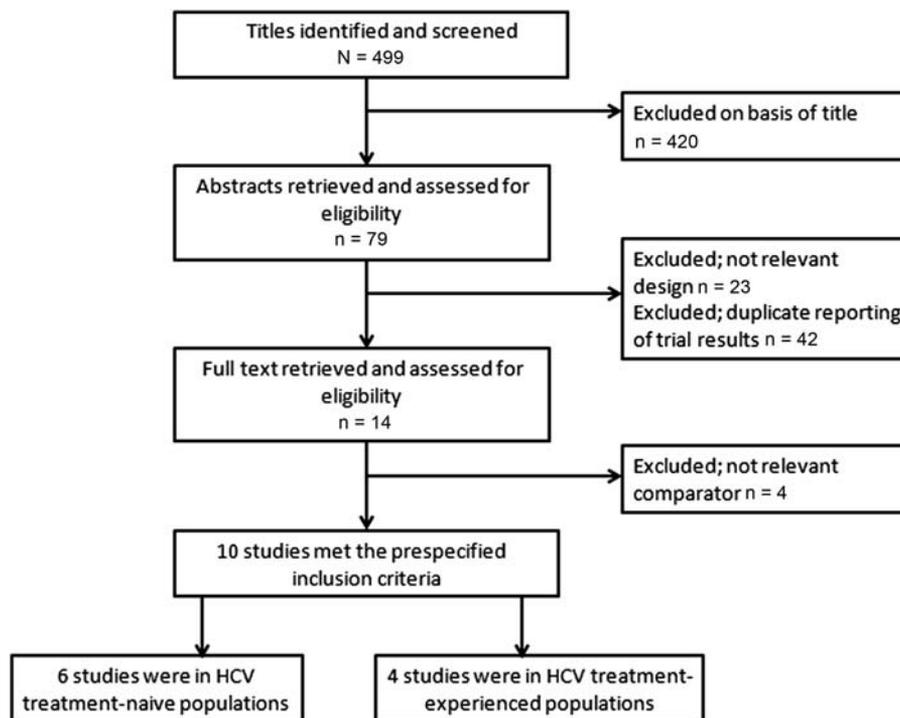
Figure 1. Flow diagram of literature search for comparison meta-analysis of treatment for hepatitis C virus. Abbreviation: HCV, hepatitis C virus.

response between the trials, which limited correlations across trials in these patients. Given the recent licensing of these medications, publication bias is difficult to assess. The number of trials is too small to draw meaningful conclusions from a funnel plot, which is therefore not presented. We examined the WHO Clinical Trials registry portal and ClinicalTrials.gov and found no evidence of registered trials that appeared to be delayed in their reporting.

Data Extraction

Data were extracted from published journal articles and conference reports using standardized data collection forms. If required data were not available in the article/conference abstract, supplemental appendices were examined. Additional information was sought directly from 5 authors, 4 of whom replied. This allowed us to analyze the quality of the studies and access data that were not available from the publications.
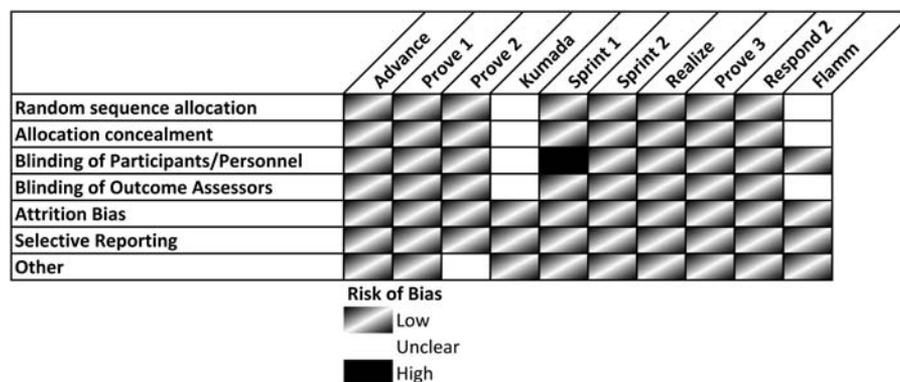

Figure 2. "Risk of bias" summary of trials included in the meta-analysis [26]. Abbreviations: PROVE, Protease Inhibition for Viral Evaluation 1 and 2; RESPOND, Retreatment With Hepatitis C Virus Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2; SPRINT, Serine Protease Inhibitor Therapy 1 and 2.

Table 2. Summary of Trials Included in the Mixed-Treatment Comparison Presenting Data Used in the Meta-Regression of Potential Confounders and the Subgroup Analysis

Study [Ref]	Population Characteristic	Intervention	HCV Load >800 000 IU/mL	Black Cohort	Prior Relapse	HCV 1a	Cirrhotic	Relapse Rate	SVR
ADVANCE [13]	Treatment naive	Telaprevir + PR n = 363	281 (77)	26 (7)	N/A	213 (59)	21 (6)	17/264 (65)	271 (75)
	N = 724	PR n = 361	279 (77)	28 (8)		208 (58)	21 (6)	51/189 (27)	158 (44)
PROVE-1 [14]	Treatment naive	Telaprevir + PR n = 158	134 (85)	15 (9)	N/A	101 (64)	Excluded	4/92 (4)	101 (64)
	N = 233	PR n = 75	69 (92)	9 (12)		50 (67)		8/35 (23)	31 (41)
PROVE-2 [18]	Treatment naive	Telaprevir + PR n = 81	73 (90)	1 (1)	N/A	31 (38)	Excluded	8/57 (14)	56 (69)
	N = 163	PR n = 82	68 (83)	2 (2)		25 (43)		10/45 (22)	38 (46)
Kumada et al [19]	Treatment naive	Telaprevir + PR n = 126	26 (21)	0	N/A	2 (1.2)	Excluded	21/113 (19)	92 (73)
	N = 189	PR n = 63	18 (29) (>700 000 IU/mL)	0	N/A	0 (0)		14/45 (31)	31 (49)
SPRINT-1 Part 1 [12]	Treatment naive	Boceprevir + PR n = 206	183 (89)	30 (15)	N/A	113 (55)	13 (6)	20/160 (13)	135 (66)
	N = 310	PR n = 104	94 (90) (>600 000 IU/mL)	16 (15)		53 (51)	8 (8)	12/53 (23)	39 (38)
SPRINT-2 [10]	Treatment naive	Boceprevir + PR n = 734	627 (92)	107 (15)	N/A	471 (64)	76 (10)	48/522 (9)	475 (65)
	N = 1097	PR n = 363	308 (85)	52 (14)		227 (63)	24 (7)	39/176 (22)	137 (38)
REALIZE [16]	Treatment experienced	Telaprevir + PR n = 530	472 (89)	19 (4)	286 (54)	239 (45)	139 (26)	52/214 (13)	346 (65)
	N = 662	PR n = 132	114 (86)	11 (8)	68 (51)	59 (45)	30 (23)	33/51 (65)	22 (17)
PROVE-3 [15]	Treatment experienced	Telaprevir + PR n = 115	106 (92)	9 (8)	42 (37)	69 (60)	19 (17)	22/80 (27)	59 (51)
	N = 229	PR n = 114	104 (91)	10 (9)	41 (36)	71 (62)	13 (11)	17/33 (52)	16 (14)
RESPOND-2 [11]	Treatment experienced	Boceprevir + PR n = 323	288 (89)	37 (11)	208 (64)	190 (59)	39 (12)	36 /238 (15)	202 (63)
	N = 403	PR n = 80	65 (81)	12 (15)	51 (64)	46 (58)	10 (13)	8/25 (32)	17 (21)
Flamm et al [17]	Treatment experienced	Boceprevir + PR n = 134	101 (75)	12 (9)	36 (27)	75 (56)	32 (24)	11/95 (12)	86 (64)
	N = 201	PR n = 67	54 (81)	8 (12)	47 (70)	38 (57)	15 (22)	7/21 (33)	14 (21)

All data are presented as No. (%).

Abbreviations: HCV, hepatitis C virus; PR, pegylated interferon and ribavirin; PROVE, Protease Inhibition for Viral Evaluation 1 and 2; RESPOND, Retreatment With HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2; SPRINT, Serine Protease Inhibitor Therapy 1 and 2; SVR, sustained virologic response.

Data were extracted by one researcher and all data used in the meta-analysis were cross-checked with the second researcher. Any discrepancies in the extracted data were resolved by reference to the original source material.

Data were extracted on prespecified baseline demographics and clinical characteristics of patients in addition to baseline viral characteristics such as viral load and genotype subtype, which may act as potential confounders [26]. Data were extracted on the number of patients in each arm of the trial and relative frequency of SVR. Study arms that evaluated telaprevir or boceprevir for unlicensed durations, or without both peg-IFN/RBV at standard doses were excluded. All articles reported intention-to-treat results and these were utilized. In the trials of treatment-naive patients, data were extracted for numbers of patients with black ethnicity. The number of patients with black ethnicity in Protease Inhibition for Viral Evaluation (PROVE-2; n = 3) and the trial by Kumada et al (n = 0) were small and separate SVR rates for this subgroup were not available; therefore, we excluded these studies from the subgroup analysis of black ethnicity [14, 19]. There were no other missing data. For patients who were treatment-experienced, data were extracted on numbers who were enrolled in the trials as prior treatment "relapsers" and those who were not. A description of the trials and data extracted is presented in Table 2.

Statistical Analysis

The analysis was conducted using a Bayesian mixed treatment comparison model. The included trials provide the underlying
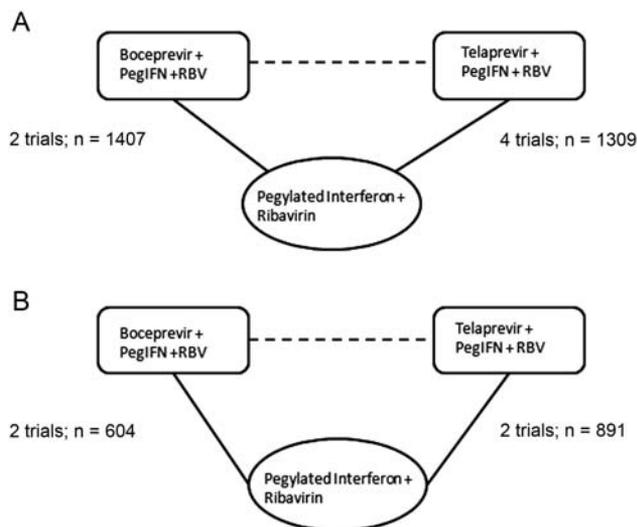
Figure 3. Network diagrams for mixed treatment comparisons. *A*, Network diagram for mixed treatment comparison in hepatitis C virus (HCV) treatment-naive patients. *B*, Network diagram for mixed treatment comparison in HCV treatment-experienced cohorts. Abbreviations: HCV, hepatitis C virus; PegIFN + RBV, pegylated interferon and ribavirin.

evidence structure for this analysis, which is shown in the network diagram in Figure 3. Models were fitted separately for 2 patient populations: treatment-naive patients and treatment-experienced patients. A subgroup analysis for black ethnicity was conducted in the naive patient group. In the experienced group, "relapsers" and "nonrelapsers" were analyzed as subgroups. A post hoc analysis of differences in relapse rates for patients who achieved an end-of-treatment response was also performed. As there are only a small number of trials for each drug, and in the absence of marked heterogeneity (Table 2), a fixed-effects model for the treatment effect was used. The influence of 3 potential confounders (baseline HCV load, HCV genotype subtype, and presence of cirrhosis) were analysed in a meta-regression model to identify if they were effect modifiers [28]. The models calculate odds ratios (ORs) of one treatment relative to another. All models were fitted in WinBUGS, a software package using Markov chain Monte Carlo techniques [22, 29]. The code can be accessed in the Supplementary Data.

RESULTS

Of the 499 studies identified by the literature searches, 10 studies met the inclusion criteria [10, 11–19]. Six studies related to treatment-naive patients, and 4 to treatment-experienced patients. The study characteristics, along with patient numbers, treatment arms, and potential confounding variables, are presented in Table 2. Baseline demographic, clinical,

and viral parameters were similar across the trials. The meta-regression found none of the potential confounders to be effect modifiers; therefore, they were not included in the final model.

Treatment-Naive Patients

Six studies met the criteria for analysis in HCV genotype 1–infected, treatment-naive patients [10, 12–14, 18–19]. In the total treatment-naive population (n = 2716), the addition of boceprevir to a backbone therapy of peg-IFN/RBV resulted in more efficacious treatment than peg-IFN/RBV alone (OR, 3.06 [95% CI, 2.43–3.87]). Similarly, the addition of telaprevir to a backbone therapy of peg-IFN/RBV resulted in more efficacious treatment than peg-IFN/RBV alone (OR, 3.24 [95% CI, 2.56–4.10]). There was insufficient evidence to detect a difference between telaprevir and boceprevir when added to standard of care (OR, 1.06 [95% CI, .75–1.47]). When patients with black ethnicity were considered (n = 283 [boceprevir n = 205, telaprevir n = 78]), increased efficacy with either of the triple-therapy regimens compared to standard of care was also observed (boceprevir vs standard of care: OR, 3.58 [95% CI, 1.84–7.31]; telaprevir vs standard of care: OR, 5.99 [95% CI, 2.17–17.87]). The model did not detect a significant difference in efficacy between either triple therapy regimen in this subpopulation (telaprevir vs boceprevir: OR, 1.67 [95% CI, .48–6.05]). Results are summarized in Figure 4.

Treatment-Experienced Patients

Four studies met the criteria for analysis in the HCV genotype 1–infected treatment-experienced patient population [11, 15–17]. In the overall treatment-experienced population (n = 1495), there was a significant improvement in SVR when the regimens including boceprevir were compared with standard of care (OR, 6.53 [95% CI, 4.20–10.32]) and when regimens containing telaprevir were compared with standard of care (OR, 8.32 [95% CI, 5.69–12.36]). There was insufficient evidence to detect a difference in SVR between those regimens utilizing telaprevir as their third agent and those utilizing boceprevir as their third agent (OR, 1.27 [95% CI, .71–2.30]).

In the model considering those patients who had prior treatment relapse (n = 841), there was a significant difference in efficacy that favored telaprevir (telaprevir vs boceprevir: OR, 2.61 [95% CI, 1.24–5.52]). Both agents were significantly better than standard of care (boceprevir vs standard of care: OR, 6.25 [95% CI, 3.79–10.53]; telaprevir vs standard of care: OR, 16.31 [95% CI, 9.52–28.51]). In patients who did not have a prior treatment relapse (n = 654), there was no significant difference in efficacy detected between telaprevir and boceprevir (OR, 0.44 [95% CI, .09–1.72]). Results are summarized in Figure 4.
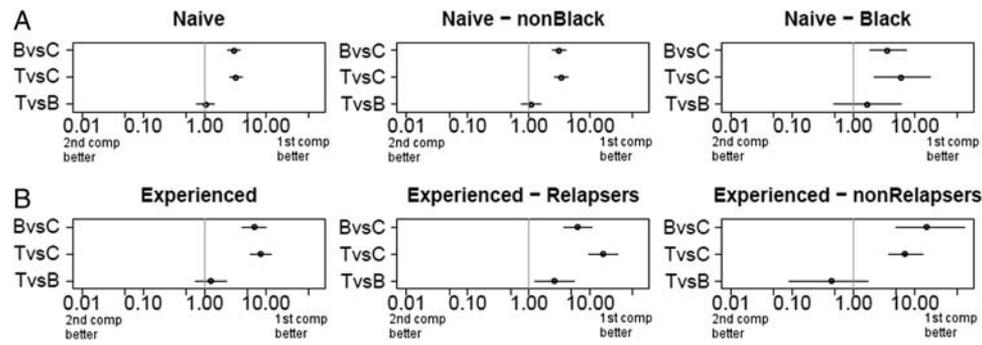
Figure 4. Summary of results. *A*, Graph for pairwise odds ratio of relative treatment effects in the overall treatment-naive population and the subgroup analysis of treatment-naive black and nonblack populations. *B*, Graph for pairwise odds ratio of relative treatment effects in the overall treatment-experienced population and the subgroup analysis of treatment-experienced "relapsers" and "nonrelapsers." Abbreviations: B, boceprevir; T, telaprevir; C, standard of care (pegylated interferon plus ribavirin); comp, comparator.

On-Treatment Analysis of Relapse Rates

For treatment-naive patients, no difference was detected in relative relapse rates between patients who received a telaprevir-based regimen and those who received a boceprevir-based regimen (OR, −0.34 [95% CI, −.53 to .22]).

For patients who were treatment-experienced, patients treated with telaprevir had a lower relative rate of relapse than those treated with boceprevir (OR, −0.91 [95% CI, −1.78 to −.03]).

Sensitivity Analysis

With the exclusion of the trials with an increased risk of bias (PROVE-2 and Kumada et al [19] for the treatment-naive analysis; Flamm et al [14] in the treatment-experienced analysis), the sensitivity analysis resulted in increased credible intervals in all analyses performed, as would be expected from the smaller numbers. The improved outcome observed with telaprevir over boceprevir in treatment experienced "relapsers" remained (OR, 2.64 [95% CI, 1.09–6.30]). There was no change to the findings in the other analyses.

DISCUSSION

The enhanced clinical efficacy with the addition of protease inhibitors to the standard of care has been clearly demonstrated in the randomized controlled trials published to date [10, 11–19]. They have shown an improvement in treatment outcomes across a broad range of patient populations, both treatment-naive and treatment-experienced. As a result of these favorable clinical trial outcomes, these agents are currently being assessed in many healthcare systems from the perspective of their cost-effectiveness. The comparative effectiveness of these agents is germane to the analysis under consideration in both pharmacoeconomic and clinical forums as decisions are made between agents in relation to funding and individual prescribing. The ideal method of addressing the question of which agent is more effective would be a head-to-head noninferiority trial. This would enable us to control for the differences between the telaprevir and boceprevir trials in relation to their use of different interferons, dosing strategies for ribavirin, and use of antianemics. However, a search of the Clinicaltrials.gov, the WHO clinical trials registry portal, and the International Standard RCT network revealed 177 registered trials for telaprevir and boceprevir, none of which was a head-to-head trial. In the absence of a noninferiority trial in the foreseeable future, the present analysis provides useful and relevant estimates of relative efficacy between these agents.

We found an improvement in the rates of SVR achieved with telaprevir over boceprevir in patients who have had a prior treatment relapse. Potential difficulties with isolating the efficacy of the individual protease inhibitors include patient tolerance to and adherence with peg-IFN/RBV. Relapsed patients have previously tolerated full courses of peg-IFN/RBV with an end-of-treatment response that lessens these concerns. Therefore, the differences in effect seen in this population may better reflect the differences between the individual protease inhibitors with less confounding from tolerance issues to peg-IFN/RBV than that seen in other patient populations. Treatment duration is also an important factor with regard to choice of agent for this population. The total treatment duration for response-guided therapy with telaprevir is shorter (24 weeks) than with boceprevir (36 weeks in the United States, 48 weeks in Europe) which has implications for cost and patient tolerance [4–5]. A post hoc analysis of patients with an

end-of-treatment response and a subsequent relapse was performed to further analyze the difference seen in the treatment-experienced population. This found a reduced relative rate of relapse in patients treated with telaprevir, which may explain some of the difference found in the "relapse" subgroup. Unfortunately, the data on relapse rates by previous treatment response were not reported for all trials, so no further analysis was possible. There are relatively small numbers of trials available for analysis at the present time, particularly in treatment-experienced patients, and future studies will be helpful to further elucidate this relationship.

While the RCTs included patients who have historically been less susceptible to treatment with interferon and ribavirin, such as those who are black, the numbers were low. However, the overall magnitude of the treatment effect was greater in the treatment-naive black subgroup than that seen in the overall population. In the subgroup of treatment-experienced "nonrelapsers," the magnitude of the treatment effects of the new regimens over the standard of care is also greater than that seen in the overall population. It is possible that the proportional benefit gained from the new agents is greater in those who are less responsive to interferon than in those who are most responsive to interferon. This would support the subgroup analysis of SPRINT-2, which revealed little difference in SVR rates in patients who were treatment-naive, noncirrhotic with a CC IL-28B subtype between those treated with peg-IFN/RBV and those given triple therapy [30]. It may be reasonable to offer some patients who fall into this category and achieve a rapid virologic response the option to continue on peg-IFN/RBV alone, given the additive side effects and costs of the protease inhibitors.

Limitations

The most robust way to evaluate this question would be a head-to-head randomized controlled noninferiority trial. At the present time, there is no plan for such a trial. Therefore, this analysis provides the best available estimates of relative efficacy. The mixed treatment comparison we have performed does not detect a significant difference in treatment outcomes between the 2 agents for the primary comparisons. The credible intervals for the estimated effects are wide, indicating remaining uncertainty. This highlights the need for additional data to accurately determine the size of the difference between these treatments, rather than there being no difference.

This analysis only included data from randomized controlled trials. Effectiveness in the standard clinical setting may not correlate with that seen in clinical trials. As these agents become more widely used, it is important that real-world effectiveness data be analyzed. The establishment of outcomes registries would facilitate this. The small number of patients in certain important clinical subgroups, such as those with

cirrhosis, precluded their separate consideration in our analysis. Individual trial data indicate that they have improved outcomes with the new agents compared with standard of care [10, 11, 15–17, 19]. The incidence of adverse effects such as rash and anemia may have an impact on the cost of and adherence to therapies; however, we have only considered efficacy in our paper.

The meta-regression found none of the potential confounders to be effect modifiers. The relative frequencies of the confounders were very similar across trials and in this study they were analyzed at the aggregate level rather than at the patient level. These factors may explain why they were not found to be significant (Table 2).

CONCLUSIONS

Our analysis does not detect a significant difference in treatment outcomes between the 2 agents in the overall treatment-naive or treatment-experienced populations. However, in patients with a history of prior treatment relapse, telaprevir has greater relative efficacy. As these patients have the potential for 24 weeks of therapy when treated with telaprevir, it would appear to be the optimal choice in this subgroup. This study was not able to provide estimates of relative efficacy for patients with cirrhosis owing to limited trial data. The results of studies currently under way may allow such analysis in the future. In the absence of head-to-head noninferiority trials, these estimates of relative efficacy will be of use to decision makers involved in cost-effectiveness assessments, and to clinicians when considered along with clinical parameters in the setting of individual patient treatment pathways.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

References

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