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

Best Practice/Intervention:	Dang SS. et al. (2012) Telaprevir for chronic hepatitis C with genotype 1: a meta-analysis. Hepato-Gastroenterology, 59(114):461-468.
Date of Review:	
Reviewer(s):	

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:** **Chronic HCV genotype 1 patients who are untreated or did not have a sustained virologic response to previous therapy** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Xi'an, China** **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 assess the effect of telaprevir in treatment-naive patients and in HCV genotype 1 patients who did not have sustained virologic response to previous therapy
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	☐	☒	☐	
Effectiveness	☒	☐	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Searched in MEDLINE, EMBASE, CENTRAL, the Web of Science and the Chinese Biomedical Database for relevant records in any language.
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?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Similar analysis could be done with similar inclusion criteria
Evidence of manpower requirements is indicated in the best practice/intervention	☒	☐	☐	Two reviewers independently screen studies for eligibility with a third reviewer available to adjudicate arising conflicts between the two reviewers.
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Hepato-Gastroenterology*
International guideline or protocol has been established	☒	☐	☐	Analysis was carried out according to the Cochran Handbook of Systematic Review
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Require account to view full article at http://www.hepatogastroenterology.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: _____	☐	☐	☐	- Found that telaprevir is effective in patients with HCV genotype 1 with respect to sustained virological response - Telaprevir shows significant higher rate of end of treatment response when combined with Peg-IFN plus ribavirin Limitations: - Only 5 RCTs included in the analysis - 2 of the 5 RCTs did not provide SVR outcomes but they have low numbers of patients so data were weighted less and results were less influenced - Compiled data lacked long-term outcomes of interventions - Further randomized trials needed to draw firmer analysis of long-term effects of telaprevir

Original Paper

Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis

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ABSTRACT

Background/Aims: The examination of HCV virological clearance through several randomized clinical trials of telaprevir in genotype 1 chronic hepatitis C. **Methodology:** We analyzed the effect of telaprevir on the end of treatment virological response and the sustained response, and investigated its harmful effect using meta-analysis of 5 randomized controlled trials. **Results:** Overall analysis revealed a significant effect of telaprevir in both naive patients (RR, 1.32; 95% CI, 1.08-1.60) and previously failed treated patients (p<0.0001). Monotherapy and double therapy seemed to show no effect in naive patients. Triple therapy followed with PegIFN-2a plus ribavirin seemed to be effective in both naive patients and previously failed treated patients. Telaprevir was associated with a significantly higher incidence of serious adverse events (RR, 1.45; 95% CI, 1.00-2.10) and with discontinuation (RR, 2.23; 95% CI, 1.40-3.55) because of adverse events. In naive patients, relapsers and non-responders, the regimen of telaprevir/ PegIFN-2a/ribavirin for 12 weeks followed by PegIFN-2a/ribavirin for 12 weeks (T12PR24) was the optimal regimen regarding to efficiency and duration. **Conclusions:** Telaprevir combined with PegIFN-2a plus ribavirin may improve sustained response in genotype 1 chronic hepatitis C. Regimen T12PR24 may be the best regimen in this respect. New randomized controlled trials are required to confirm this meta-analysis.

Key Words: Telaprevir; Hepatitis C; Genotype 1; Meta-analysis.

Abbreviations: Sustained Response (SR); End Of Treatment Response (ETR); Interferon (IFN); Non-structural 3/4A (NS3/4A); Randomized Controlled Trial (RCT); Relative Risk (RR); Confidence Interval (CI); Telaprevir/PegIFN-2a/Ribavirin for 12 weeks, followed by Placebo/PegIFN-2a/Ribavirin for 12 weeks (T12PR24); Telaprevir/PegIFN-2a/Ribavirin for 24 weeks, followed by PegIFN-2a/Ribavirin for 24 weeks (T24PR48); Telaprevir/PegIFN-2a for 24 weeks (TP24); Placebo/PegIFN-2a/Ribavirin for 24 weeks, followed by PegIFN-2a/Ribavirin for 24 weeks (PR48); Telaprevir/PegIFN-2a/Ribavirin for 12 weeks, followed by Placebo/PegIFN-2a/Ribavirin for 36 weeks (T12PR48); Telaprevir/PegIFN-2a/Ribavirin for 12 weeks (T12PR12); Telaprevir/PegIFN-2a for 12 weeks (T12P12).

INTRODUCTION

Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV) (1). HCV is a major public health problem and a leading cause of chronic liver disease. Currently, an estimated 180 million people are infected worldwide (2). About 50-80% of patients with primary HCV infection develop chronic infection; about 25% of patients with chronic infection develop cirrhosis within 10 to 30 years; and 5-10% of patients with cirrhosis develop hepatocellular carcinoma (HCC) (3).

More than ten years ago, interferon (IFN) therapy provide a sustained virological response (SR) in 15-20% of patients with chronic hepatitis C. Combining ribavirin with IFN improved the SR to 40% (4) and until recently has been the most effective therapy. Several factors influence the rate of SR. In naive HCV patients with genotype 1, which is the predominant genotype in Europe and North America, the SR is about 40-50%, whereas an SR is observed in 80% of patients with genotype 2 or 3. Patients who do not have an SR to the combination therapy have a low likelihood of success with retreatment, only 12-22% (5-8). Therefore, the development of effective regimens is required, especially in patients who did not have an SR to previous therapy.

Telaprevir, also known as VX-950, has been developed to treat hepatitis C. It is an orally bioavailable inhibitor of the non-structural 3/4A (NS3/4A) HCV serine protease, an enzyme required for viral replication (9,10). Recently, some controlled clinical trials have shown that telaprevir treatment appears to be promising. However, its effect varied depending on how it was combined with IFN, with or without ribavirin, and treatment duration.

We were unable to identify any systematic reviews or meta-analysis addressing the effects of telaprevir for patients with chronic hepatitis C. In this systematic review, we sought to assess both the beneficial and harmful effect of telaprevir. For this purpose, we used an evidence-based approach consisting of meta-analysis of randomized controlled trials (RCT). We assessed its antiviral efficiency in untreated patients and in patients who did not have an SR to previous therapy in order to identify an optimal regimen for each type of patient.

METHODOLOGY

Literature search

We searched MEDLINE, EMBASE, CENTRAL, the Web of Science and the Chinese Biomedical Database to September 8 2010 for relevant records in any language. Our search included the gray literature (conference proceedings, dissertations and theses) through ARTICAL-FIRST, PAPERFIRST and PROQUEST. We searched bibliographies of relevant reviews and all included trials, and checked the clinical trial registry (www.clinicaltrials.gov) for additional studies. Search terms were: telaprevir, vx-950, hepatitis C, HCV and random*.

Criteria for inclusion and exclusion of studies

Studies were considered if they met the following criteria: (a) randomized controlled trial regardless of blinding, number of patients randomized, or publication

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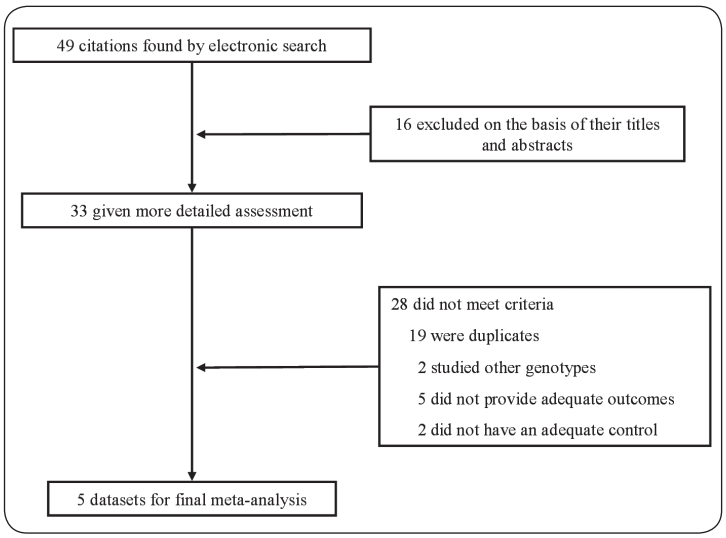

FIGURE 1. Flow diagram of search strategy and study selection.

status; (b) male or female patients, of any age or ethnic origin, who had chronic genotype 1 HCV infection; (c) telaprevir administered at any dose, duration and route administration, given separately or in combination *versus* no intervention, placebo or other intervention.

Exclusion criteria were (a) non-human studies; (b) non-randomized trials; (c) studies in HIV and HCV co-infected patients; (d) studies in liver transplantation; (e) studies using telaprevir with a design that did not allow the real assessment of the effect of telaprevir.

Outcome measures

Primary outcome assessed was viral response defined as loss of detectable HCV RNA, including SR and end of treatment response (ETR). Secondary outcome assessed was adverse events and discontinuation.

Data extraction and quality assessment

Two reviewers (W.W., X.W.) independently screened all records by title or abstract for those requiring further retrieval (full text or abstract), and then independently

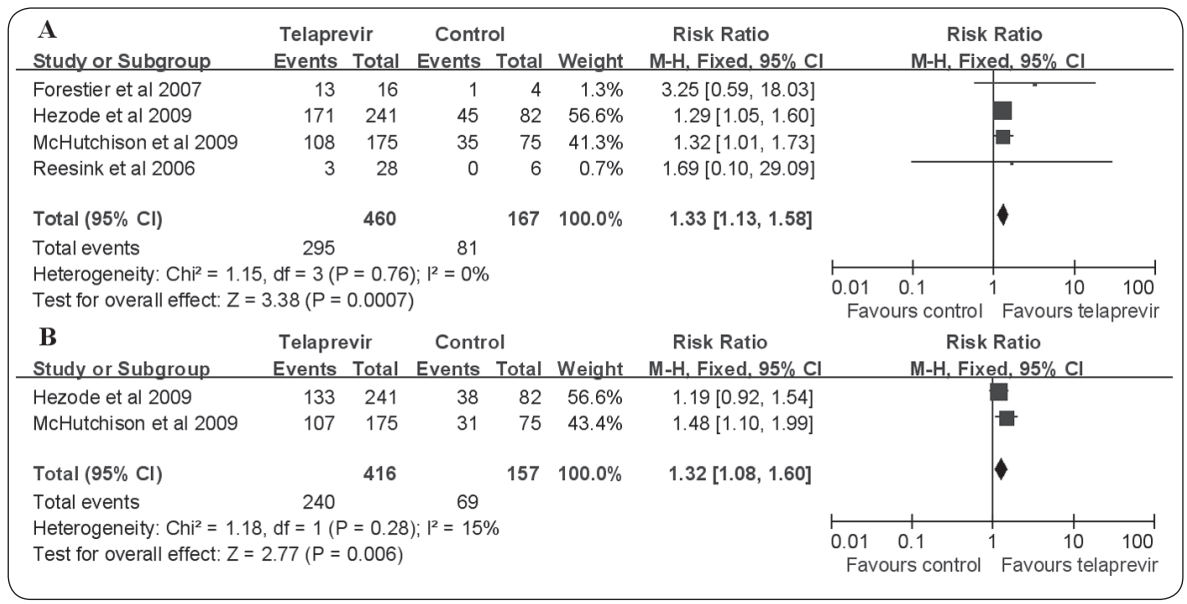

FIGURE 2. Overall analysis of RCTs evaluating the effect of telaprevir (**A**) on the end of treatment response and (**B**) sustained response.

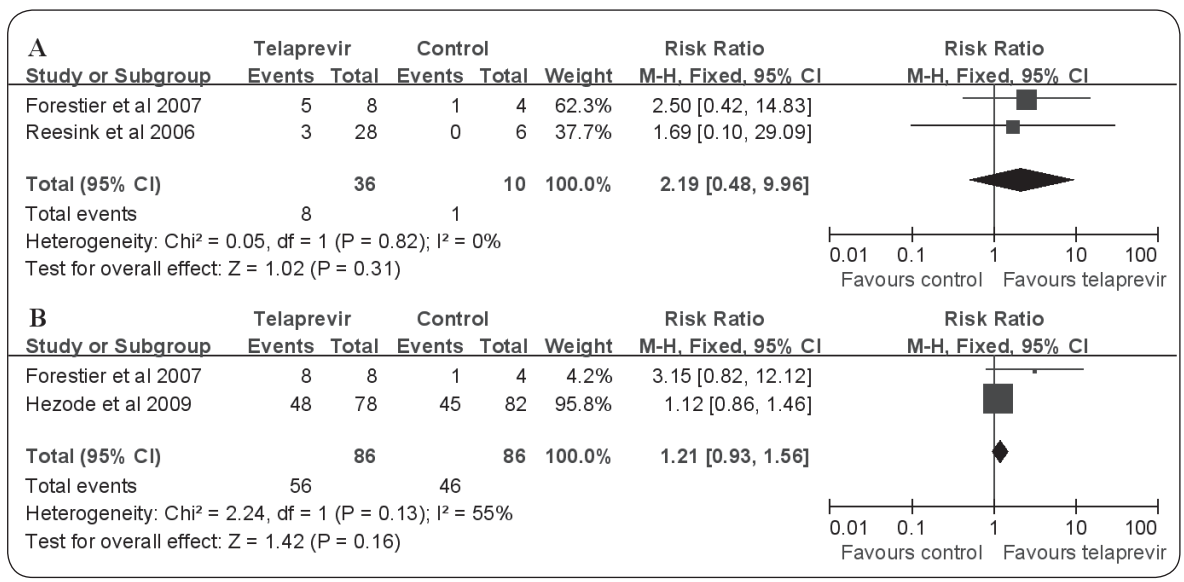

FIGURE 3. RCTs evaluating the effect of telaprevir double therapy on the end of (**A**) treatment response and (**B**) sustained response in naive patients.

reviewed these studies for eligibility. A third reviewer (S.D.) was available to adjudicate on any conflicts arising between the two reviewers. We wrote to the primary authors for further information regarding study inclusion, methods, outcomes, and verification of trial results. We recorded patient eligibility, number of patients, and treatment in each group.

We addressed methodological quality including adequacy of random sequence generation, allocation concealment, blinding, loss of follow-up, selective reporting or other biases. Judgment regarding the presence of methodological biases was made according to the Cochran criteria guidelines (11).

Data synthesis and analysis

We used statistical package RevMan 5.0.24 and the analysis was carried out according to the Cochran Handbook of Systematic Review. Dichotomous data were presented as relative risk (RR) with 95% confidence intervals (CIs). The fixed-effect model was used, with significance set at p=0.05. Study heterogeneity was determined using the p value from the chi-square (χ^2) test and the I^2 statistic in which 0-40% may be unimportant heterogeneity, 30-60% indicates moderate, 50-90% indicates substantial and 75-100% indicates considerable heterogeneity. Where data were only available from one trial, we used the χ^2 test for dichotomous data.

RESULTS

Search results

Figure 1 shows our search and selection process. Our search produced 49 records (12-60). Of these 49, 16 were clearly irrelevant to this review and were excluded on the basis of their titles and abstracts. Of the remaining 33 records (14,19,22-25,28-34,36-38,40-44,46-52,54-57,60), 28 were excluded: 19 (19,22,25,30,31,33,34,36-38,42-44,47,49,51,54,57,60) were duplicate studies, 2 (29,32) studied other genotypes, 5 (40,46,48,50,52) did not provide adequate outcomes, and 2 (24,41) did not have an adequate control. Finally, 5 studies (14,23,28,55,56) were eligible for inclusion.

Study characteristics

The five randomized trials were published as full text articles and included 1080 patients. The sample size of each arm within the trials varied, ranging from 4 to 115 patients. The majority of the patients were males. In four trials (23,28,55,56), patients were previously untreated and only one trial (14) involved patients who did not have an SR to previous therapy. Nearly all patients were infected with HCV genotype 1, and 5% with unknown genotype. One trial (56) studied telaprevir monotherapy at 3 dosage, and the other four trials (14,23,28,55) studied telaprevir plus IFN with or without ribavirin using similar dosage (telaprevir: 1125mg or 1250mg loading dose, then 750mg every 8 hours; PegIFN-2a: 180μg per week; ribavirin: 1000-1200mg per day, according to body weight). The duration of treatment varied, ranging from 2 to 48 weeks. In three trials (14,23,28), follow-up was at least 24 weeks after completion of treatment to assess the rate of SR, while in the other two trials (55,56) follow-up was not long enough so only ETR was reported. **Table 1** shows characteristics of the five RCTs included.

Risk of bias in included studies

Table 2 reports the risk of bias for each trial. Although all studies described randomization, one (56) did not adequately describe methods of random sequence generation, and four (14,23,28,56) did not adequately describe allocation concealment. All studies used blinding methods for outcome measures, although the outcome measurement was not likely to be influenced by lack of blinding. In all studies, there was a description of follow-up and withdrawals/dropouts. Two studies (55,56) failed to include results for a key outcome. Three trials (14,23,28) reported power calculations to assess sample size.

Effect on overall naive patients or overall patients who did not have an SR to previous therapy

Four RCTs (23,28,55,56) evaluated telaprevir's effect on ETR and two RCTs (23,28) on SR in naive patients. In overall naive patients, using a fixed-model analysis, telaprevir was associated with a significantly higher rate of ETR (RR, 1.33; 95% CI, 1.13 to 1.58) and SR (RR 1.32, 95% CI 1.08 to 1.60) than control therapy (**Figure 2**). In the McHutchison *et al.* 2010 trial, the only trial which evaluated patients who did not have an SR to previous therapy, telaprevir was also associated with a significantly higher rate of ETR (223/339 in the telaprevir group *versus* 34/114 in the control group, p<0.0001 using the χ^2 test) and SR (146/339 in the telaprevir group *versus* 16/114 in the control group, p<0.0001 using the χ^2 test) than in IFN plus ribavirin for overall patients.

Subgroup analysis of telaprevir effect in naive patients

In naive patients, two RCTs (55,56) evaluated the effect of telaprevir monotherapy on ETR. They both had a small sample size in each group, and telaprevir did not show a significantly higher rate of ETR (RR, 2.19; 95% CI, 0.48-9.96) than placebo. Two RCTs (28,55) evaluated the effect of telaprevir combined with IFN on ETR and one RCT on SR *versus* IFN plus ribavirin. The results did not show that telaprevir combined with IFN had a statistically significantly better effect on either ETR (RR, 1.21; 95% CI, 0.93-1.56) or SR (RR 0.77, 95% CI 0.53 to 1.13) (**Figure 3**).

Telaprevir is not effective when used on its own or when only combined with PegIFN, but when combined with PegIFN plus ribavirin presented a significantly higher rate of ETR than recommended PR48 regardless of T12PR12 (RR, 1.48; 95% CI, 1.22-1.79), T12PR24 (RR, 1.25; 95% CI, 1.04-1.52) or T12PR48 (χ^2 test, p=0.025). The rate of SR was also significantly improved in T12PR24 (RR, 1.48; 95% CI, 1.20-1.83) and in T12PR48 (χ^2 test, p=0.001) but not in T12PR12 (RR, 1.19; 95% CI, 0.91-1.56). When comparing T12PR24 and T12PR48 in one RCT, neither ETR nor SR was significantly different (**Figure 4**).

Subgroup analysis of telaprevir effect in previously failed treated patients

Only one RCT (14) studied telaprevir effect in patients who did not have an SR to previous therapy (including relapse, non-response, and breakthrough), and dichotomous data was analyzed using the χ^2 test. The rates of ETR in three telaprevir groups (76% in the T12PR24 group, 67% in the T24PR48 group, and 54% in the T24P24 group) were significantly higher than the rate in the control group (30% in the PR48 group). The rates of SR in the three telaprevir groups (51% in the

TABLE 1. Study characteristics of randomized controlled trials included in the meta-analysis.

Source	Regimen	Patients (n)	ERT (n)	SR (n)
McHutchison *et al.* 2010 (14)	Arm 1: telaprevir/PegIFN-2a/ribavirin for 12 weeks, followed by placebo/PegIFN-2a/ribavirin for 12 weeks (T12PR24)	115	87	59
	Arm 2: telaprevir/PegIFN-2a/ribavirin for 24 weeks, followed by PegIFN-2a/ribavirin for 24 weeks (T24PR48)	113	76	60
	Arm 3: telaprevir/PegIFN-2a for 24 weeks (TP24)	111	60	27
	Arm 4: placebo/PegIFN-2a/ribavirin for 24 weeks, followed by PegIFN-2a/ribavirin for 24 weeks (PR48)	114	34	16
McHutchison *et al.* 2009 (23)	Arm 1: telaprevir/PegIFN-2a/ribavirin for 12 weeks, followed by placebo/PegIFN-2a/ribavirin for 12 weeks (T12PR24)	79	45	48
	Arm 2: telaprevir/PegIFN-2a/ribavirin for 12 weeks, followed by placebo/PegIFN-2a/ribavirin for 36 weeks (T12PR48)	79	51	53
	Arm 3: telaprevir/PegIFN-2a/ribavirin for 12 weeks (T12PR12)	17	12	6
	Arm 4: placebo/PegIFN-2a/ribavirin for 12 weeks, followed by PegIFN-2a/ribavirin for 36 weeks (PR48)	75	35	31
Hezode *et al.* 2009 (28)	Arm 1: telaprevir/PegIFN-2a/ribavirin for 12 weeks, followed by placebo/PegIFN-2a/ribavirin for 12 weeks (T12PR24)	81	57	56
	Arm 2: telaprevir/PegIFN-2a/ribavirin for 12 weeks (T12PR12)	82	66	49
	Arm 3: telaprevir/PegIFN-2a for 12 weeks (T12P12)	78	48	28
	Arm 4: placebo/PegIFN-2a/ribavirin for 12 weeks, followed by PegIFN-2a/ribavirin for 36 weeks (PR48)	82	45	38
Forestier *et al.* 2007 (55)	Arm 1: telaprevir/PegIFN for 2 weeks, followed by PegIFN/ribavirin for 12 weeks	8	8	NA
	Arm 2: telaprevir for 2 weeks, followed by PegIFN/ribavirin for 12 weeks	8	5	NA
	Arm 3: placebo/PegIFN for 2 weeks, followed by PegIFN/ribavirin for 12 weeks	4	1	NA
Reesink *et al.* 2006 (56)	Arm 1: telaprevir 1250mg q12h for 2 weeks	10	0	NA
	Arm 2: telaprevir 450mg q8h for 2 weeks	10	1	NA
	Arm 3: telaprevir 750mg q8h for 2 weeks	8	2	NA
	Arm 4: placebo for 2 weeks	6	0	NA

In parentheses are regimen abbreviations; NA: not available.

TABLE 2. Assessment of study quality.

Source	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias
McHutchison *et al.* 2010	Yes	Unclear	Yes	Yes	Yes	Yes
McHutchison *et al.* 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Hezode *et al.* 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Forestier *et al.* 2007	Yes	Yes	Yes	Yes	No	Yes
Reesink *et al.* 2006	Unclear	Unclear	Yes	Yes	No	Yes

TABLE 3. Meta-analysis of adverse events in the telaprevir group *vs.* the control group.

Adverse Event	Studies	Patients	Statistical Method	Effect Estimate	*p*	Heterogeneity
Rash	4	1046	Risk Ratio (M-H, Random, 95% CI)	1.68 (1.19,2.37)	0.003	p=0.05, I^2=61%
Pruritus	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	1.94 (1.55, 2.44)	<0.00001	p=0.27, I^2=23%
Hemorrhoids	2	703	Risk Ratio (M-H, Fixed, 95% CI)	6.95 (2.59, 18.64)	0.0001	p=0.49, I^2=0%
Nausea	4	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.34 (1.12, 1.60)	0.001	p=0.15, I^2=43%
Diarrhea	3	755	Risk Ratio (M-H, Random, 95% CI)	1.14 (0.53, 2.47)	0.74	p<0.0001, I^2=90%
Pyrexia	3	755	Risk Ratio (M-H, Random, 95% CI)	0.88 (0.56, 1.38)	0.58	p=0.08, I^2=60%
Fatigue	2	555	Risk Ratio (M-H, Fixed, 95% CI)	0.90 (0.77, 1.05)	0.17	p=0.30, I^2=8%
Anemia	3	755	Risk Ratio (M-H, Random, 95% CI)	1.39 (0.85, 2.30)	0.19	p=0.07, I^2=62%

T12PR24 group, 53% in the T24PR48 group, and 24% in the T24P24 group) were also significantly higher than the rate in the control group (14% in the PR48 group).

To find out which regimen was most efficient, we compared the three telaprevir groups. The T12PR24 group and the T24PR48 group both had significantly higher rates of SR than the T24P24 group ($p<0.0001$ and $p<0.0001$, respectively), while no significant difference was found between the T12PR24 group and the T24PR48 group ($p=0.786$).

In patients with a previous relapse, the three telaprevir groups all had significantly higher rates of SR than the control group. The T12PR24 group and the T24PR48 group had significantly higher rates of SR than the T24P24 group ($p=0.015$ and $p=0.002$, respectively), while no significant difference was found between the T12PR24 group and the T24PR48 group ($p=0.504$).

In patients with previous non-response, the T12PR24 group and the T24PR48 group (but not the T24P24 group) had significantly higher rates of SR than the control group ($p<0.0001$, $p<0.0001$ and $p=0.640$, respectively), while no significant difference was found between the T12PR24 group and the T24PR48 group ($p=0.824$).

Only a few breakthrough patients were recruited in the trial, so statistical analysis was not available to assess the intervention effect on these patients.

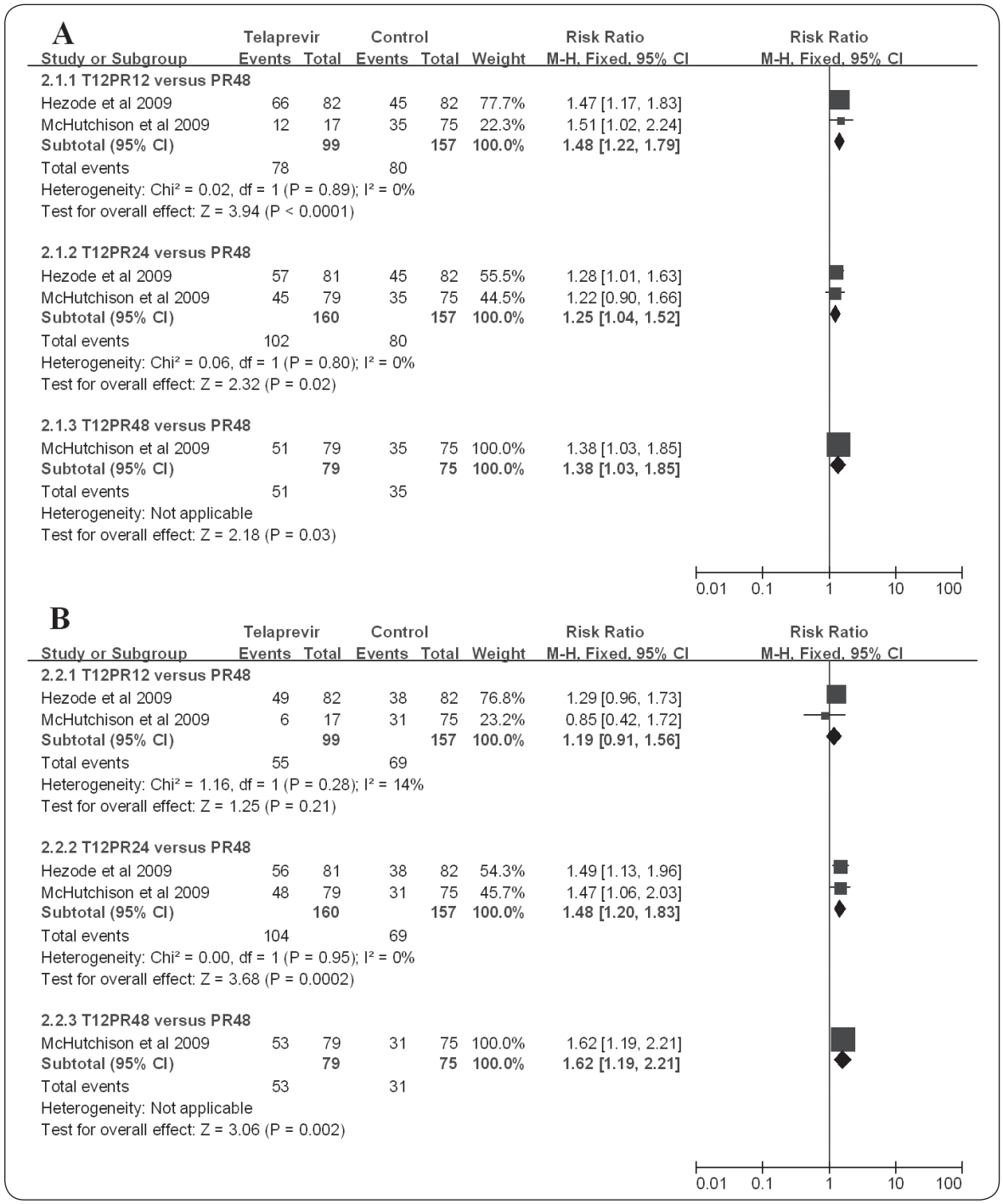

FIGURE 4.
RCTs comparing the effect of regimens with telaprevir triple therapy on the end of (**A**) treatment response and (**B**) sustained response in naive patients.

Adverse events and discontinuation because of adverse events

Two small sample-sized RCTs (55,56) did not report serious adverse events in either the telaprevir group or the control group. The other three RCTs (14,23,28) reported the number of patients who developed serious adverse events in each group. Combining the results of the three RCTs demonstrated that there was a significant effect of telaprevir on serious adverse events (RR, 1.45; 95% CI, 1.00-2.10). However, non-serious adverse event data were not reported per patient, so some patients may have experienced more than one adverse event. Therefore, these data are count data, not dichotomous data. As such, meta-analysis of total adverse events was not possible. However, data for a certain kind of adverse event was often reported, which made meta-analysis of the particular kind of adverse event available. The meta-analysis shows that telaprevir was associated with a significantly higher incidence of rash, pruritus, hemorrhoids and nausea (**Table 3**).

Overall, the telaprevir group showed significantly more discontinuation because of adverse events than the control group (RR, 2.23; 95% CI, 1.40-3.55).

DISCUSSION

After combining all sorts of telaprevir regimens, our meta-analysis found that telaprevir was associated with a higher rate of SR than in control, both in naive patients and previously failed treated patients. However, in naive patients, we did not find that telaprevir monotherapy or double therapy produced an improved rate of SR *versus* control. This may be due to small-sized samples in the monotherapy or double therapy groups. In fact, not all telaprevir/IFN/ribavirin regimens induced a higher rate of SR than the recommended IFN + ribavirin regimen. The regimen telaprevir/PegIFN-2a/ribavirin for 12 weeks without followed PegIFN-2a/ribavirin did not improve SR, although it improved ETR. However, longer duration of followed PR may not induce higher rates of SR, as 48 weeks and 24 weeks of followed PR did not show a significant difference in the rate of SR. Regarding efficiency and duration, the T12PR24 regimen may be the best regimen for chronic hepatitis C in genotype 1 naive patients according to the recent RCTs.

In previously failed treated patients, of which the majority were relapsers and non-responders, double therapy with telaprevir did not seem to improve SR. Two regimens of triple therapy with telaprevir (T12PR24 and T24PR48) improved SR *versus* the recommended PR regimen. However, the T24PR48 regimen, which had a longer duration of telaprevir and IFN plus ribavirin treatment than the T12PR24 regimen, did not further improve SR, regardless of relapsers or non-responders. Regarding efficiency and duration, the T12PR24 regimen may be the best regimen for chronic hepatitis C in genotype 1 relapsers or non-responders according to the recent RCTs.

We found that telaprevir intervention was associated with a significant increase in serious adverse events and with discontinuation because of adverse events. Increased adverse events such as rash, pruritus, hemorrhoids and nausea were also likely due to telaprevir. From the available data in only one trial (14) it was difficult to estimate the effects of duration of intervention therapy on the incidence of adverse events. In the analysis of these data, we found that adverse events and the discontinuation because of adverse events were more common in long-duration therapy, although they were not statistically significant. Therefore, the T12PR24 regimen appeared to provide a better risk-benefit profile than the T24PR48 regimen.

However, there were several factors which limited the context of our results. Firstly, only 5 RCTs could be included in the review. Secondly, our compiled data lacked the long-term outcomes of intervention, such as liver histology, the incidence of endstage liver disease or requirement for liver transplantation and liver-related mortality. However, no clinical trials assessing these outcomes have been carried out. Finally, 2 RCTs (55,56) did not supply SR, one of the most important outcomes. However, because of their low numbers of patients, they were less weighted and results were less influenced. Although the total number of patients included in this review seems sufficient in underlining the effects telaprevir, more trials are required: to confirm its treatment effect; to identify any adverse events associated with it; and to assess the effect of telaprevir on subgroups of patients regarding factors influencing treatment effect (such as other genotype, ALT level, cirrhosis, *etc*.).

In summary, this meta-analysis of five RCTs indicates that telaprevir is an effective therapy in naive patients, relapsers, and non-responders with genotype 1 chronic hepatitis C with respect to virological sustained response, albeit with higher rates of discontinuation because of adverse events. The T12PR24 regimen may have been the optimal treatment regimen for HCV. It is advisable to carry out more randomized trials in order to draw a firmer analysis of the long-term effects of telaprevir.

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