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

Best Practice/Intervention:	Qin H. et al. (2012) Safety of telaprevir for chronic hepatitis C virus infection: a meta-analysis of randomized controlled trials. *Clinical Drug Investigation*, 32(10):665-672.
Date of Review:	March 2, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population: HCV patients treated with telaprevir-based therapy** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin: 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; review of randomized clinical trials to assess the safety of telaprevir in combination with Peg-IFN and ribavirin therapy for the treatment of hepatitis C patients.
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☐	☒	☐	Two literature comparing the efficacy of telaprevir was excluded from the study
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:	☒	☐	☐	Relevant studies identified through a search of electronic databases with no language limitations
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?	☐	☒	☐	Due to high cost and drug approval regulations, telaprevir may not be readily available in some 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 Drug Investigation*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Available to download with a cost from http://link.springer.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 study was not funded

Other relevant information: _____	☐	☐	☐	- Cautious use of telaprevir is warranted - Potential for increased risks of adverse events with the use of telaprevir

ORIGINAL RESEARCH ARTICLE

Clin Drug Investig 2012; 32 (10): 665-672
1173-2563/12/0010-0665/$49.95/0

Safety of Telaprevir for Chronic Hepatitis C Virus Infection

A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Previous studies have reported telaprevir is effective for chronic hepatitis C virus infection, but the safety of a telaprevir-based regimen remains uncertain.

Objective: A meta-analysis was performed to assess the safety of the addition of telaprevir to a standard regimen of pegylated interferon (peginterferon) plus ribavirin (combination telaprevir with peginterferon plus ribavirin, the TPR group) compared with the standard regimen group (peginterferon plus ribavirin, the PR group).

Methods and Results: Seven randomized controlled trials involving a total of 2808 patients were included in the meta-analysis. The addition of telaprevir to the standard regimen was associated with a significantly increased risk of serious adverse events compared with the standard PR group (relative risk [RR] = 1.56; 95% confidence interval [CI] 1.21, 2.03; $p = 0.0007$; $I^2 = 0\%$). Telaprevir was also associated with increased risk of treatment discontinuation (RR = 2.10; 95% CI 1.56, 2.83; $p < 0.0001$; $I^2 = 42\%$). In addition, telaprevir was more likely to cause nausea (RR = 1.39; $p < 0.0001$), diarrhoea (RR = 1.32; $p = 0.004$), pruritus (RR = 1.56; $p = 0.0006$), rash (RR = 1.60; $p < 0.0001$) and anaemia (RR = 1.55; $p = 0.007$). There was no difference in the other kinds of adverse events between the two groups. Sensitivity analysis further validated the credibility of the above outcomes.

Conclusion: Our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse events associated with the use of telaprevir among patients with chronic hepatitis C virus infection, and cautious use of telaprevir is warranted.

Introduction

Telaprevir (VX-950) is an oral inhibitor of the non-structural 3/4A (NS3/4A) hepatitis C virus (HCV) serine protease that specifically targets the NS3/4A HCV serine protease to cause rapid reduction in HCV RNA levels for the treatment of chronic hepatitis C.[1,2] Recent phase II or phase III studies suggested that 12 weeks treatment with telaprevir, along with different durations of ribavirin treatment, induced higher sustained virological response (SVR) compared with the standard pegylated interferon (peginterferon) plus ribavirin regimen.[3-5] However, apart from the expected interferon (IFN)-related and ribavirin-related systemic symptoms, some adverse events, such as rash and pruritus, were prominent in the groups that received telaprevir.[6-8] As previously noted, patients who received telaprevir-based therapy were more likely to discontinue treatment because of an adverse event than were controls, who received peginterferon-α-2a and ribavirin alone.[4,5] However, there was an obvious inconsistency in the estimate of the risk of adverse effects caused by telaprevir-based therapy across those studies.[6-8] Meta-analysis is a statistical procedure for combining results from previously published studies to acquire a more precise estimation of the clinical interventions.[9] Hence, to provide the most comprehensive assessment of the safety profile of the addition of telaprevir to a standard regimen of peginterferon plus ribavirin in patients with chronic HCV infection, we performed a meta-analysis of all available randomized controlled trials (RCTs).

Methods

Search Strategy and Selection of Studies

Relevant studies were identified and selected by searching databases including PubMed (updated to September 2011), EMBASE (from 1980 to September 2011) and China Biology Medicine (CBM) using the search words ('Telaprevir' or 'VX-950') and ('hepatitis C' or 'HCV') and ('randomized controlled trial' or 'randomized' or 'random' or 'RCT'). No language or date limitations were imposed. The following selection criteria of included studies were applied: (i) randomized controlled trial; (ii) patients with chronic hepatitis C according to established diagnostic criteria; (iii) compared the standard PR regimen group (24- to 48-week course of peginterferon plus ribavirin, PR group) to the addition of telaprevir to the standard PR regimen group (combination of telaprevir with the standard regimen of peginterferon plus ribavirin, TPR group). Duplicated publications or publications without available data were excluded.

Data Extraction and Quality Assessment

Data were extracted from each study with a pre-designed review form as follows: authors, published year, study design, patients' basic characteristics, adverse events, serious adverse events, and treatment discontinuation events. Adverse events included fatigue, pyrexia, nausea, diarrhoea, pruritus, rash and other common adverse events according to previous studies.[10-12] Serious adverse events were defined as grade 3 or higher or more adverse events according to data from included RCTs.[10-12] The assessment of study quality was performed using the Jadad system, which evaluated studies by assessing randomization, blinding and a description of withdrawals or dropouts.[13] Both the data extraction and quality assessment were independently performed by two researchers and any disagreement was resolved by consensus among all researchers.

Statistical Methods

The risk ratios (RRs) with 95% confidence intervals (CIs) of each clinical event from eligible studies were pooled and presented to assess the safety profile of the addition of telaprevir to a standard 24- to 48-week course of peginterferon plus ribavirin (TPR group). In this meta-analysis, two models for dichotomous outcomes including the random-effects model and the fixed-effects model were conducted. The random-effects model was conducted using the DerSimonian and Laird method, and the fixed-effects model was conducted using the Mantel-Haenszel method.[14,15] To assess the between-study heterogeneity more precisely, heterogeneity testing was performed by

calculating both the Q statistic to test for heterogeneity and the I^2 statistic to quantify the between-study heterogeneity.[16,17] Heterogeneity was considered significant for $p < 0.10$ (Q statistic), and the random-effects model was used to pool the results. If heterogeneity was not significant, $p > 0.10$ (Q statistic), the fixed-effects model was used to pool the results. In addition, sensitivity analysis was performed to validate the credibility of outcomes by sequential omission of individual studies.[18] A funnel plot was used as an analytical tool to quantify the potential presence of publication bias; an asymmetric plot suggested possible publication bias. All analyses were performed using version 5.1 of Review Manager Software (RevMan 5.1, Cochrane Collaboration, Oxford, England). All p-values were two-sided and a p-value of less than 0.05 was deemed statistically significant.

Results

Study Characteristics

A flow diagram illustrating the study selection process is shown in figure 1. The search strategy generated 37 records, of which nine full-text publications were further assessed for eligibility.[6-8,10-12,19-21] After reviewing each original paper and extracting data, two articles were excluded, including one comparing the different efficacy of telaprevir given every 8 or 12 hours combined with the standard peginterferon plus ribavirin regimen,[20] and one study comparing the efficacy of telaprevir in combination with peginterferon-α2-a and ribavirin for 24 or 48 weeks.[11] Finally, seven RCTs involving a total of 2808 patients with chronic HCV infection were included in this meta-analysis.[6-8,10,12,19,21]

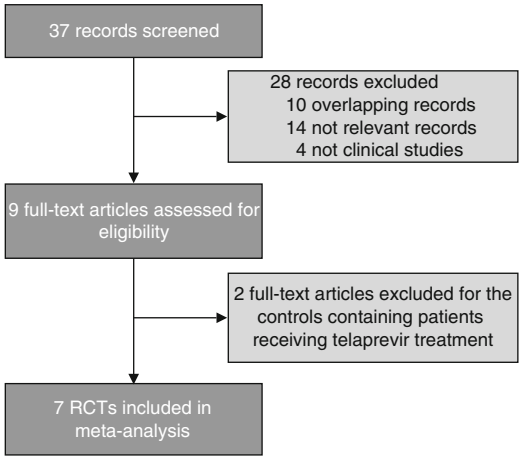

Fig. 1. Flowchart of selection of studies for inclusion in the meta-analysis. **RCT** = randomized controlled trial.

There were a total of 1963 patients randomized to the TPR group and 845 patients randomized to the PR group. The HCV genotype in six RCTs was HCV genotype 1, and the other one was HCV genotype 2 and HCV genotype 3. All RCTs were well designed and six RCTs scored 5 points on the Jadad scoring system,[6-8,10,12,19] while the other one scored 3 points.[21]

Safety Profile Evaluation

Table I shows the summary of the meta-analysis on safety profile evaluation. Telaprevir was associated with a significantly increased risk of serious adverse events compared with the standard PR group (RR = 1.56; 95% CI 1.21, 2.03; $p = 0.0007$; $I^2 = 0\%$) [figure 2]. Patients who received telaprevir-based therapy were more likely to discontinue treatment because of an adverse event than the controls, who received peginterferon-α-2a and ribavirin alone (RR = 2.10; 95% CI 1.56, 2.83; $p < 0.0001$; $I^2 = 42\%$) [figure 3]. Telaprevir was significantly more likely to cause nausea (RR = 1.39; $p < 0.0001$), diarrhoea (RR = 1.32; $p = 0.004$), pruritus (RR = 1.56; $p = 0.0006$), rash (RR = 1.60; $p < 0.0001$) and anaemia (RR = 1.55; $p = 0.007$). There was no difference in the other kinds of adverse events between those two groups (table I). Sensitivity analysis showed that the significance of pooled RRs of these adverse events remained robust after omission of any individual study, which validated the credibility of the study outcomes.

In the subgroup analyses according to telaprevir treatment period, telaprevir for 12 weeks was also associated with a significantly increased risk of serious adverse events (RR = 1.50; 95% CI 1.13, 1.98; $p = 0.004$; $I^2 = 0\%$) [figure 2] and

Table I. Characteristics of RCTs included in the meta-analysis

Study [reference]	Study design	TPR group[a]	PR group[a]	HCV genotype	Quality score
McHutchison et al.[6]	Phase IIb RCT	T12PR12 (17 patients), T12PR24 (79 patients) and T12PR48 (79 patients)	PR48 (75 patients)	1	5
Hezode et al.[8]	Phase IIb RCT	T12PR24 (81 patients) and T12PR12 (82 patients)	PR48 (82 patients)	1	5
McHutchison et al.[12]	Phase IIb RCT	T12PR24 (115 patients) and T24PR48 (113 patients)	PR48 (114 patients)	1	5
Jacobson et al.[7]	Phase III RCT	T12PR12 (363 patients) and T8PR8 (364 patients)	PR48 (361 patients)	1	5
Zeuzem et al.[10]	Phase III RCT	T12PR48 (539 patients)	PR48 (132 patients)	1	5
Kumada et al.[19]	Phase IIIb RCT	T12PR24 (126 patients)	PR48 (63 patients)	1	5
Foster et al.[21]	Phase IIa RCT	T2PR2 (14 patients)	PR2 (18 patients)	2 and 3	3

a Numerals after abbreviations of drug names represent weeks of treatment.

HCV = hepatitis C virus; **peginterferon** = pegylated interferon; **PR** = peginterferon-α-2a or α-2b plus ribavirin; **RCT** = randomized controlled trial; **T** = telaprevir; **TPR** = combination telaprevir with peginterferon plus ribavirin.

increased risk of discontinuing treatment because of an adverse event (RR = 1.93; 95% CI 1.40, 2.67; $p < 0.0001$; $I^2 = 10\%$) [figure 3]. Furthermore, telaprevir for 12 weeks was also significantly more likely to cause nausea (RR = 1.39; $p < 0.0001$), diarrhoea (RR = 1.23; $p = 0.02$), pruritus (RR = 1.50; $p < 0.0001$), rash (RR = 1.56; $p < 0.0001$) and anaemia (RR = 1.58; $p = 0.005$). Sensitivity analysis showed that the significance of pooled RRs of these adverse events remained robust after omission of any individual study, which also validated the credibility of outcomes. However, the subgroup analyses of telaprevir for 24 weeks were not further performed owing to only one relevant study having been published to date.

Publication Bias

To assess the effects of publication bias in this meta-analysis, a funnel plot was employed and the symmetry of the funnel plot is clear (see figure 4), which indicates that there was no obvious publication bias in this meta-analysis.

Discussion

There are approximately 180 million individuals infected with HCV worldwide, and this can progressively result in hepatic injury, liver cirrhosis and hepatocellular carcinoma.[22,23] Telaprevir is widely used to treat HCV.[3] Recent phase II or phase III studies suggested that telaprevir could increase the SVR rate when it was combined with peginterferon plus ribavirin in patients with chronic HCV infection. However, there was an obvious inconsistency in the estimate of the risk of adverse effects caused by telaprevir-based therapy across those studies and the safety of a telaprevir-based regimen remained uncertain.[24,25] Hence, to provide the most comprehensive assessment of the safety of the addition of telaprevir to a standard regimen of peginterferon plus ribavirin, we performed this meta-analysis by including seven RCTs (a total of 2808 patients with chronic HCV infection). The pooled results suggested telaprevir was associated with a significantly increased risk of serious adverse events compared with the standard PR group (RR = 1.56; 95% CI 1.21, 2.03; $p = 0.0007$; $I^2 = 0\%$) and risk of discontinuing treatment because of an adverse event than the controls who received peginterferon-α-2a and ribavirin alone (RR = 2.10; 95% CI 1.56, 2.83; $p < 0.0001$; $I^2 = 42\%$). In addition,, telaprevir was also significantly more likely to cause nausea (RR = 1.39; $p < 0.0001$), diarrhoea (RR = 1.32; $p = 0.004$), pruritus (RR = 1.56; $p = 0.0006$), rash (RR = 1.60; $p < 0.0001$) and anaemia (RR = 1.55; $p = 0.007$). There was no difference in the other kinds of adverse events between the two groups (table II). Sensitivity analysis showed that the significance of pooled RRs of these adverse events remained robust after omission of any

individual study, which validated the credibility of outcomes. Subgroup analyses of telaprevir for 12 weeks also further confirmed the above results (table II).

Our results showed that there were increased risks of nausea, diarrhoea, pruritus, rash and anaemia in the telaprevir group compared with the PR group (all p-values were less than 0.01); however, there was no difference in other adverse events between those two groups (table II). There was also an increased risk of serious adverse events in the telaprevir group compared with the PR group (RR = 1.56; 95% CI 1.21, 2.03; p = 0.0007; I^2 = 0%) [table II, figure 2], and the significance of pooled RRs remained robust when sensitivity analysis was performed by omitting any individual study, suggesting that the outcome was credible. Thus, our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse events associated with the use of telaprevir among patients with chronic HCV infection. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system is an emerging system of rating the quality of evidence and the grading strength of recommendations in systematic reviews, health technology assessments, and clinical practice guidelines addressing alternative management options.[26,27] According to the GRADE system, the quality of evidence for serious adverse events and treatment discontinuation are both high, suggesting that further studies are very unlikely to change our confidence in the estimate of effect.[26,27] Thus, there is high-quality evidence

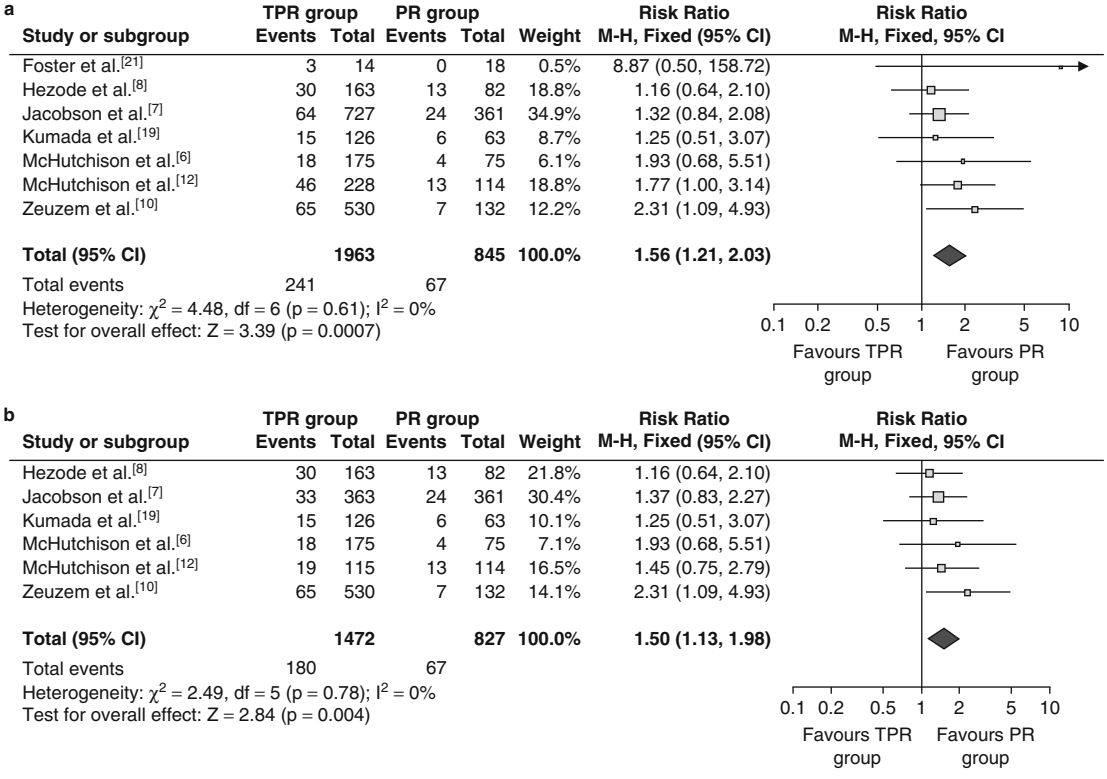

Fig. 2. Forest plot of meta-analysis of serious adverse events in the TPR group compared with the PR group: (**a**) pooled data for all seven RCTS; (**b**) pooled data for six trials with 12-week data. **CI** = confidence interval; **df** = degrees of freedom; **I^2** = percentage of the total variation across studies due to heterogeneity; **M-H** = Mantel-Haenszel; **peginterferon** = pegylated interferon; **PR** = peginterferon plus ribavirin; **TPR** = combination telaprevir with peginterferon plus ribavirin; **Z** = test of overall treatment effect.

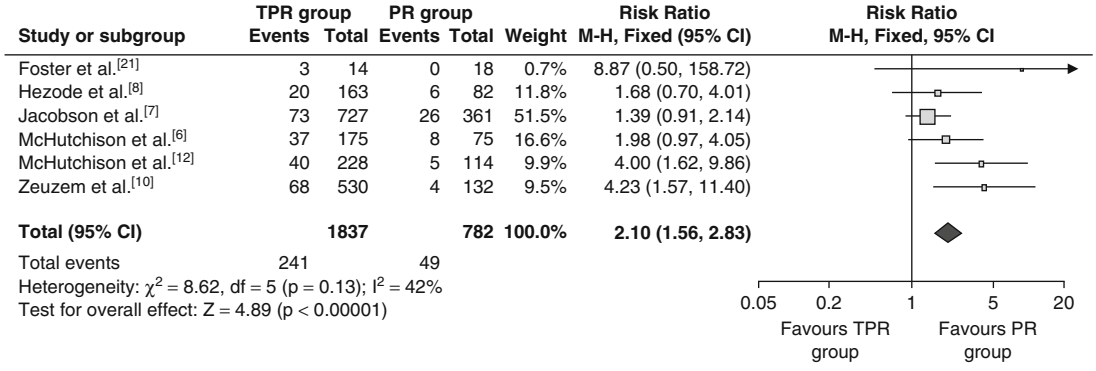

Fig. 3. Forest plot of meta-analysis of discontinued treatment because of an adverse event in the TPR group compared with the PR group. **CI** = confidence interval; **df** = degrees of freedom; **I²** = percentage of the total variation across studies due to heterogeneity; **M-H** = Mantel-Haenszel; **peginterferon** = pegylated interferon; **PR** = peginterferon plus ribavirin; **TPR** = combination telaprevir with peginterferon plus ribavirin; **Z** = test of overall treatment effect.

for an increased risk of serious adverse events associated with the use of telaprevir among patients with chronic HCV infection, and this evidence should be taken into account when considering use of telaprevir in patients with a high propensity and risk for serious adverse events.[28,29] Wise use of telaprevir is therefore warranted, including appropriate selection of candidates for therapy, close monitoring of drug adherence, appropriate management of adverse effects and early application of discontinuation protocols.[30]

Previous studies suggest that polymorphisms near the interleukin 28B (*IL28B*) gene not only predict treatment-induced and spontaneous recovery from HCV infection, but also appear to predict improved SVR rate in response to standard therapy with peginterferon and ribavirin.[31-33] As patients with the *IL28B* rs8099917 CC genotype have an approximately 80% SVR rate, triple therapy might not be necessary in these patients and will be less cost effective and associated with more adverse effects.[31-33] Furthermore, while the *IL28B* rs8099917 CC genotype appears to be predictive of a shorter duration of therapy, the TT genotype conversely is associated with longer duration of therapy and may be associated with more adverse effects.[33] Thus, *IL28B* polymorphism testing may be necessary for patients treated with triple therapy and may be predictive of adverse effects.[33]

There were some limitations to this meta-analysis. There were obvious inconsistencies in the telaprevir treatment regimen including different durations of total treatment period (12–48 weeks) and different durations of telaprevir treatment period (12–24 weeks). The duration of the telaprevir treatment period can have an additional influence on the safety profile of telaprevir because the longer duration of telaprevir treatment might cause more adverse events.[12] The durations of the total treatment period in those RCTs were also different from each other, which can influence the outcomes. In addition, the long-term safety profile of the addition of telaprevir was not reported in all the RCTs, especially in terms of the long-term prognosis of those patients, which

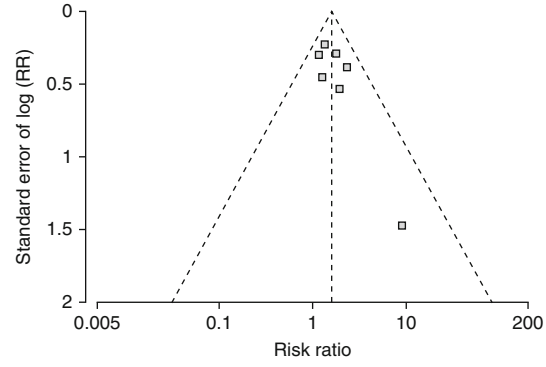

Fig. 4. Funnel plot for assessing publication bias among the seven included studies. **RR** = risk ratio.

Table II. Safety profile evaluation of telaprevir-based regimen for chronic hepatitis C virus infection

Analysis items	RR (TPR vs PR)		Heterogeneity		Model
	RR (95% CI)	p-Value[a]	I^2 (%)	p-Value[b]	
All studies					
Serious adverse events[c]	1.56 (1.21, 2.03)	0.0007	0	0.61	Fixed
Treatment discontinuation	2.10 (1.56, 2.83)	<0.0001	42	0.13	Fixed
Fatigue	1.02 (0.94, 1.10)	0.65	21	0.28	Fixed
Pyrexia	1.06 (0.92, 1.21)	0.43	41	0.13	Fixed
Nausea	1.39 (1.23, 1.58)	<0.0001	25	0.25	Fixed
Diarrhoea	1.32 (1.13, 1.54)	0.0004	48	0.10	Fixed
Pruritus	1.56 (1.21, 2.01)	0.0006	58	0.03	Random
Rash	1.60 (1.26, 2.03)	<0.0001	59	0.03	Random
Headache	0.96 (0.87, 1.07)	0.49	45	0.11	Fixed
Dizziness	1.02 (0.70, 1.50)	0.91	9	0.29	Fixed
Anaemia	1.55 (1.13, 2.13)	0.007	77	0.0005	Random
Neutropenia	1.14 (0.68, 1.92)	0.61	78	0.03	Random
Cough	0.86 (0.64, 1.15)	0.31	0	0.49	Fixed
Dyspnoea	1.26 (0.82, 1.93)	0.29	0	0.32	Fixed
Myalgia	0.83 (0.58, 1.18)	0.31	0	0.60	Fixed
Arthralgia	0.74 (0.50, 1.10)	0.14	0	0.34	Fixed
Depression	0.92 (0.68, 1.25)	0.58	0	0.68	Fixed
Insomnia	1.07 (0.93, 1.22)	0.36	22	0.27	Fixed
Studies with 12-week data					
Serious adverse events[c]	1.50 (1.13, 1.98)	0.004	0	0.78	Fixed
Treatment discontinuation	1.93 (1.40, 2.67)	<0.0001	10	0.35	Fixed
Fatigue	1.02 (0.93, 1.11)	0.72	44	0.13	Fixed
Pyrexia	0.98 (0.85, 1.14)	0.83	23	0.29	Fixed
Anaemia	1.58 (1.15, 2.18)	0.005	77	0.002	Random
Headache	0.93 (0.78, 1.11)	0.40	54	0.07	Random
Pruritus	1.50 (1.31, 1.71)	<0.0001	47	0.11	Fixed
Rash	1.56 (1.36, 1.80)	<0.0001	40	0.15	Fixed
Diarrhoea	1.23 (1.04, 1.45)	0.02	9	0.35	Fixed
Nausea	1.39 (1.21, 1.59)	<0.0001	46	0..12	Fixed

a For RR (TPR vs RR).

b For heterogeneity test (Q statistic test).

c Serious adverse events were defined as grade 3 or higher adverse events according data from included RCTs.

I^2 = percentage of the total variation across studies due to heterogeneity; **peginterferon** = pegylated interferon; **PR** = peginterferon plus ribavirin; **RCT** = randomized controlled trial; **RR** = risk ratio; **TPR** = combination telaprevir with peginterferon plus ribavirin.

also needs further study. Genotype differences in the resistance development of HCV may affect the susceptibility to adverse effects, and this aspect also needs further study.[34,35]

Conclusion

Our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse events associated with the use of telaprevir in patients with chronic HCV infection, and cautious use of telaprevir is warranted.

Acknowledgements

The authors have no conflicts of interest that are directly relevant to this study. No external funding was received for the conduct of this study.

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