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Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis

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Objectives: To assess the beneficial and harmful effects of telaprevir for patients with genotype 1 chronic hepatitis C. ***Methods:*** We searched Cochrane Central Register of Controlled Trials (Issue 4, 2012), MEDLINE, EMBASE, Chinese Biomedical Database (CBM), CNKI database and Chinese WanFang Database between 1980 and May 2012. Randomized clinical trials assessing telaprevir in combination with peginterferon alfa and ribavirin versus no intervention or placebo in combination with peginterferon alfa and ribavirin in patients with genotype 1 chronic hepatitis C were included. The primary outcome measure was viral response, including sustained virologic response and virologic response at the end of treatment. The secondary outcome measures were relapse rate, severe adverse events, treatment discontinuation and commonly reported adverse events. ***Results:*** Six trials with 2,775 participants were included. Telaprevir in combination with peginterferon alfa and ribavirin seemed to show a significant effect on sustained virologic response, virologic response at the end of treatment and relapse rate in naive patients and previously unsuccessfully treated patients, except T12PR12 which seemed without beneficial effect on sustained virologic response (Odds Ratio (OR) 1.41; 95% CI 0.83 to 2.40) and relapse rate (Odds Ratio (OR) 1.55; 95% CI 0.71 to 3.36) in naive patients. It also was associated with a significantly higher incidence of severe adverse events (Odds Ratio (OR) 2.15, 95% CI1.29 to 3.58) and treatment discontinuation (Odds Ratio (OR) 4.79, 95% CI1.72 to 13.37) because of adverse events in previously unsuccessfully treated patients, but not in naive patients. ***Conclusions:*** Telaprevir in combination with peginterferon alfa and ribavirin has been recommended as option for the treatment of genotype 1 chronic hepatitis C. It has been considered as effective to improve viral response and reduce relapse rate in patient who suffer genotype 1 chronic hepatitis C. However, the treatment should be monitored carefully as it may cause some severe adverse events. For further confirmation of its treatment effect and clarify its possible adverse events, more randomized clinical trials need to be carried out.

1. Introduction

Hepatitis C is a viral infection which causes swelling (inflammation) of the liver (Choo et al. 1989; Germer et al. 1999). Globally, it is estimated that approximately 170 million people are chronically infected with hepatitis c virus, nearly 4.1 million persons were infected with hepatitis c virus in the United States between the years 1999 and 2002 (Memon and Memon 2002; Wasley and Alter 2000; Williams 2006). However, no risk factors can be identified in some cases (Alter et al. 1992; Roudot-Thoraval et al. 1997). Most people do not know they are infected with hepatitis C because of few symptoms. Approximately 80% of patients acquiring acute hepatitis C virus fail to clear the virus which will lead to chronic hepatitis C (Armstrong et al. 2006; Thomas and Seeff 2005). Almost 20% of these patients will finally develop cirrhosis, and 1–4% of the patients with

Abbreviations: T12PR24, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks; followed by Placebo/Pegifn-2a/Ribavirin for 12 weeks; T24PR48, Telaprevir/Pegifn-2a/Ribavirin for 24 weeks; followed by Pegifn-2a/Ribavirin for 24 weeks; PR48, Placebo/Pegifn-2a/Ribavirin for 24 weeks; followed by Pegifn-2a/Ribavirin for 24 weeks; T12PR48, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks; followed by Placebo/Pegifn-2a/Ribavirin for 36 weeks; T12PR12, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks; T12PR, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks; followed by Pegifn-2a/Ribavirin for 12 weeks if HCV RNA was undetectable at weeks 4 and 12 or for 36 weeks if HCV RNA was detectable at either time point; T8PR, Telaprevir/Pegifn-2a/Ribavirin for 8 weeks and Placebo/Pegifn-2a/Ribavirin for 4 weeks; followed by 12 or 36 weeks of Pegifn-2a/Ribavirin on the basis of the same HCV RNA criteria; Lead-in T12PR48, Peg-interferon/ribavirin for 4 wk; followed by telaprevir for 12 wk and peg-interferon and ribavirin up to a total of 48 wk.

cirrhosis may develop hepatocellular carcinoma (HCC) per year. (Lauer and Walker 2001)

Until recently, the recommended treatment for chronic hepatitis c virus infection was the combination of peginterferon and ribavirin (Ghany et al. 2009). It is reported that the sustained virologic response rates are 80–90% in hepatitis c virus genotype 2 or 3, but only 50% in hepatitis c virus genotype 1, the most prevalent genotype in Europe and North America (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). In addition, the combination therapy could not show effectiveness for many patients groups, such as patients on long-term hemodialysis (Yim 2001). Furthermore, treatment may cause some side effects, complications, and poor patient tolerability (Brok et al. 2005; Perni et al. 2006). Owing to the insufficient treatment success, new medication and therapies are needed.

Recently, telaprevir has been approved for treatment of patients with genotype 1 (G1) chronic hepatitis C by the US Food and Drug Administration (FDA). Trials have reported that telaprevir could improve sustained virologic response rates and shorten treatment duration when it is used in combination with peginterferon and ribavirin for naive patients and previously unsuccessfully treated patients with genotype 1 chronic hepatitis C (Gentile et al. 2010; Lin et al. 2006; Poynard et al. 1996). However, depending on treatment duration and treatment experience, it has shown various effects including adverse reactions as well. To our knowledge, interesting information for telaprevir therapy in genotype 1 (G1) chronic hepatitis C is available from one meta-analysis in which 5 randomized clinical trials were analysed (Dang et al. 2012). This research result has confirmed the effect of telaprevir, but no other meta-analysis on telaprevir for genotype 1 (G1) chronic hepatitis C or Cochrane systematic reviews have been published up to now, although several recently published studies have updated knowledge about effects of telaprevir in patients with genotype 1 chronic hepatitis C. As a better treatment regimen is still urgently demanded by the patients, we did this extended meta-analysis.

2. Investigations and results

2.1. Data sources

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (Issue 4,2012), MEDLINE, EMBASE, Chinese Biomedical Database (CBM), CNKI database and Chinese WanFang Database between 1980 and May 2012 using the search terms telaprevir, incivek, vx-950, Hepatitis C, chronic, hepatitis C, hep C, HCV, CHC, randomi*, and clinical trial. We also identified trials through manual searches of bibliographies in relevant articles and through hand searches of conference proceedings.

2.2. Inclusion and exclusion criteria

Randomized clinical trials assessing telaprevir in combination with peginterferon alfa and ribavirin *versus* no intervention or placebo in combination with peginterferon alfa and ribavirin in patients with genotype 1 chronic hepatitis C were included, without regarding sex, age and ethnic origin. The patients who had decompensated liver disease, another cause of clinically significant liver disease, hepatocellular carcinoma, undergone liver transplantation, and co-infection with hepatitis B or HIV were excluded.

2.3. Outcome measures

The primary outcome measures were viral response including sustained virologic response (defined as an undetectable plasma HCV RNA level 24 weeks after the last planned dose of study drugs) and virologic response at the end of treatment (defined as an undetectable plasma HCV RNA at the end of treatment). Secondary outcome measures were: (i) relapse rate (defined as an undetectable HCV RNA at the time of completion of treatment but detectable levels during the follow-up period); (ii) severe adverse events, the definition of serious adverse event was according to the International Conference on Harmonisation Expert Working Group (ICH) Guidelines (International Conference on Harmonisation Expert Working Group 1997); (iii) treatment discontinuations (defined as the discontinuation of all study drugs simultaneously during the set treatment period); (iiii) commonly reported adverse events, including anemia, neutropenia, rash and pruritus.

2.4. Methodological quality of trials assessment

Quality criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.6 (Higgins and Green 2011) was strictly followed to assess the risk of bias of each trial: such as adequate sequence generation, allocation concealment, blinding, selective outcome reporting and other sources of bias. Any disagreements were resolved by consensus. We categorized each criteria as 'yes', 'no', or 'unclear', and the summary assessments of the risk of bias for each important outcome within and across studies as 'low risk of bias', 'unclear risk of bias' and 'high risk of bias'.

2.5. Data extraction

Data were extracted independently by two reviewers. Any disagreements were resolved by consensus. We contacted authors of the eligible studies to request any missing data if needed for further analysis. From each trial we extracted setting, year, treatment experience, total sample size, arm, number of male, age, total treatment duration, methodological quality of the trial, and the outcome measures as described above.

2.6. Data synthesis

Following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011) and the Cochrane Hepato-Biliary Group Module (Gluud et al. 2011), we performed meta-analyses, and used the Review Manager 5.1 for the analyses (The Nordic Cochrane Centre 2011). We analyzed the data by intention to treat including all patients irrespective of compliance or follow-up. Both random-effects model (DerSimonian and Laird 1986) and fixed-effect model (Demets 1987) were used for analyzing data. If both models provide the same result regarding statistical significance, we only present the results of the fixed-effect model. Odds ratios (OR) with 95% confidence intervals (CI) were used to analyze the outcomes. Heterogeneity was explored by the chi-squared test, with significance set at a P value of 0.10, and heterogeneity was measured by I^2 (Higgins et al. 2003). The funnel plots or other analytical methods were used to assess potential bias, which depended on the number of clinical trials included (Egger et al. 1997).

2.7. Subgroup analyses

We would aim to perform subgroup analyses in order to explore the effect of size differences as follows:

(1) Different treatment duration;

(2) Treatment experience: naive patient or previously unsuccessfully treated patient.

2.8. Search results

We identified 1,004 references through the electronic searches of Cochrane Central Register of Controlled Trials in the Cochrane Library (n = 15), MEDLINE (n = 132), EMBASE (n = 529), CNKI database (n = 278), Chinese Biomedical Database (CBM) (n = 24) and Chinese WanFang Database (n = 26). Manual searches of article bibliographies and conference proceedings did not identify any additional studies. No quasi-randomized studies were identified. We excluded duplication articles, clearly irrelevant references, non-clinical studies, or had study objectives different articles (n = 991). 13 potentially relevant articles were retrieved for further assessment. Finally, 7 articles were excluded: one study was not a randomized controlled trial and the others did not correspond with the prespecified comparisons of the review. Accordingly, 6 articles fulfilled the inclusion criteria. All included trials were published as full papers. The flow chart of the literature search is shown in Fig. 1.

2.9. Characteristics of included studies

Six trials with 2,775 participants were included. All of them had parallel group design. In included trials, patients were followed for one week to forty eight weeks after the end of treatment. Four trials (Hezode et al. 2009; Jacobson et al. 2011; Kumada et al. 2012; McHutchison et al. 2009) included naive patients, two trials (McHutchison et al. 2010; Zeuzem et al. 2011) included patients previously treated unsuccessfully. The range of age of the patients reported in all included trials was from 18 to 70 years. One trial (McHutchison et al. 2009) randomized patients to four different intervention arms (T12PR24 versus T12PR48 versus T12PR12 versus PR48), one trial (Hezode et al. 2009) randomized patients to four different intervention arms (T12PR24 versus T12PR12 versus T12P12 versus PR48), one trial (McHutchison et al. 2010) randomized patients to four different intervention arms (T12PR24 versus T24PR48 versus TP24 versus PR48), one trial (Zeuzem et al. 2011) randomized patients to three different intervention arms (T12PR48 versus lead-in T12PR48 versus PR48), one trial (Jacobson et al. 2011) randomized patients to three different intervention arms (T12PR versus T8PR versus PR), one trial (Kumada et al. 2012) randomized patients to two different intervention arms (T12PR24 versus PR48) (Table 1).

The dose of telaprevir was 750 mg every 8 hours in three trials (Jacobson et al. 2011; Kumada et al. 2012; Zeuzem et al. 2011), 1250 mg on day 1, then 750 mg every 8 hours in two trials (Hezode et al. 2009; McHutchison et al. 2009), 1125-mg loading dose, then 750 mg every 8 hours in one trial (McHutchison et al. 2010). The duration of therapy with telaprevir ranged from 1 to 24 weeks. The dose of peginterferon alfa-2a was given as weekly 180 μg subcutaneous injections in five trials (Hezode et al. 2009; Jacobson et al. 2011; McHutchison et al. 2009; McHutchison et al. 2010; Zeuzem et al. 2011). The dose of peginterferon-a2b was given as weekly 1.5 μg/kg (range: 1.250–1.739 μg/kg) subcutaneous injections in one trial (Kumada et al. 2012). The duration of therapy with peginterferon alfa was 12 to 48 weeks. The dose of ribavirin was 1000 or 1200 mg per day, according to body weight in five trials (Hezode et al. 2009; Jacobson et al. 2011; McHutchison et al. 2009; McHutchison et al. 2010; Zeuzem et al. 2011). The daily dose of ribavirin was adjusted to the body weight (600 mg for ≤60 kg; 800 mg for > 60 kg ~80 kg; and 1000 mg for > 80 kg) in one trial (Kumada et al. 2012). The duration of therapy with ribavirin was 12 to 48 weeks.

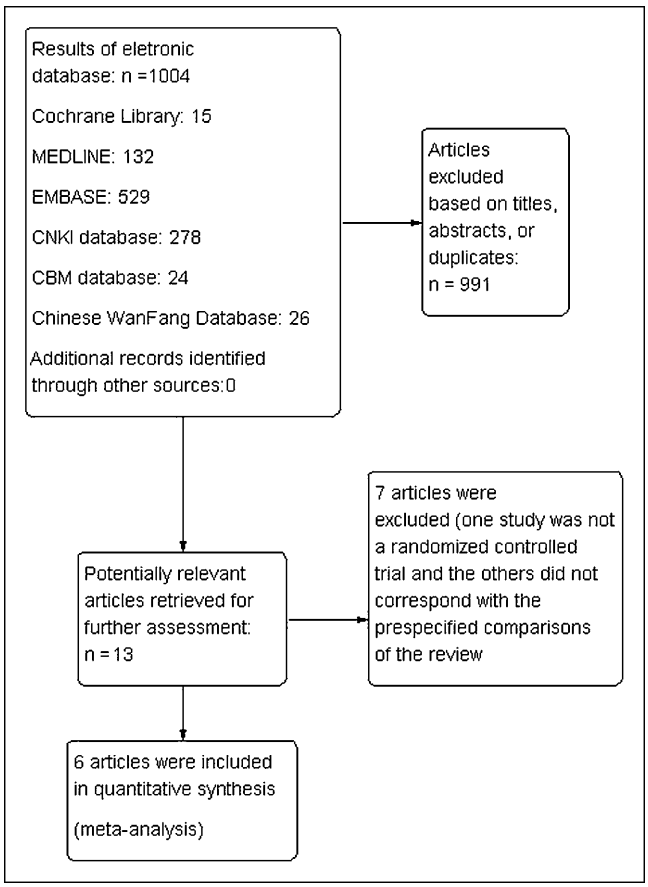

Fig. 1: Study flow diagram

2.10. Risk of bias in included studies

In two trials (Hezode et al. 2009; Zeuzem et al. 2011), the generation of allocation sequence was performed through a central telephone-based system. In four trials (Jacobson et al. 2011; Kumada et al. 2012; McHutchison et al. 2009), the generation of allocation sequence was described as randomized but the method was not specified. In 2 trials (Hezode et al. 2009; Zeuzem et al. 2011), the allocation sequence was concealed through the use of a central telephone-based system or an interactive voice-response system. In the other trials (Jacobson et al. 2011; Kumada et al. 2012; McHutchison et al. 2009, 2010), they were described as randomized but the method of allocation concealment was not specified. In 5 trials (Hezode et al. 2009; Jacobson et al. 2011; McHutchison et al. 2009, 2010; Zeuzem et al. 2011), telaprevir placebo tablets were used for blinding. In one trial (Kumada et al. 2012), blinding was not described. Only in two trials (Jacobson et al. 2011; Zeuzem et al. 2011), protocol was available in order to assess selective outcome reporting, but most of the trials reported data for the relevant primary outcomes. In one trial (Kumada et al. 2012), the number and reasons for missing patients were not described in the text. Four trials (Jacobson et al. 2011; McHutchison et al. 2009, 2010; Zeuzem et al. 2011) had adequate follow-up and clearly described the numbers and reasons for dropouts and withdrawals. Three trials (Hezode et al. 2009; McHutchison et al. 2009, 2010) were supported by Vertex Pharmaceuticals, two trials (Jacobson et al. 2011; Zeuzem et al. 2011) were supported by Vertex Pharmaceuticals and Tibotec. The baseline characteristics were similar among the treatment groups in all of the included trials (Table 2).

2.11. Effects of interventions

Owing to different treatment duration and treatment experience, we could not perform overall meta-analysis by pooling

Table 1: Characteristics of included studies

Reference	Setting/Year	Naïve/Previously Failed Treated	Total Sample Size (No.)	Arm	Male Sex–No (%)	Years of Age — Median (Range)	Total Treatment Duration
				Arm 1(T12PR24): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks, followed by placebo/peg-interferon -2a/ribavirin for 12 weeks;	54 (67)	46 (19–65)	24 weeks
				Arm 2(T12PR12): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks;	49 (60)	44 (22–65)	12 weeks
Hèzode et al. (2009)	Europe/ (2006–2007)	Naïve	244	Arm 3(PR48): Placebo/peg-iterferon -2a/ribavirin for 12 weeks, followed by peg-interferon -2a/ribavirin for 36 weeks	46 (56)	45 (18–64)	48 weeks
McHutchison et al. (2009)	US/2006	Naïve	250	Arm 1(T12PR24): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks, followed by placebo/peg-interferon -2a/ribavirin for 12 weeks;	54 (68)	49 (21–61)	24 weeks
				Arm 2(T12PR48): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks, followed by placebo/peg-interferon -2a/ribavirin for 36 weeks;	48 (61)	50 (26–61)	48 weeks
				Arm 3(T12PR12): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks;	12 (71)	49 (34–63)	12 weeks
				Arm 4(PR48): Placebo/peg-interferon -2a/ribavirin for 12 weeks, followed by peg-interferon -2a/ribavirin for 36 weeks	43 (57)	49 (24–59)	48 weeks
Kumada et al. (2011)	Japan/ (2008–2010)	Naïve	189	Arm 1(T12PR24): Telaprevir, peg-interferon/ribavirin for 12 weeks, followed by peg-interferon/ribavirin for 12 weeks;	66 (52.4)	53.0 (20–65)	24 weeks
				Arm 2(PR48): Peg-interferon and ribavirin for 48 weeks	33 (52.4)	55.0 (20–65)	48 weeks
Jacobson et al. (2011)	International/ not reported	Naïve	1088	Arm 1(T12PR): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks, followed by peg-interferon - ribavirin alone for 12 weeks;	214 (59)	49 (19–69)	48 weeks
				Arm 2(T8PR): Telaprevir/peg-interferon/ribavirin for 8 weeks and placebo/peg-interferon/ribavirin for 4 weeks, followed by 12 or 36 weeks of peg-interferon/ribavirin;	211 (58)	49 (19–68)	48 weeks
				Arm 3(PR): Placebo/peg-interferon/ribavirin for 12 weeks, followed by 36 weeks of peg-interferon/ribavirin	211 (58)	49 (18–69)	48 weeks
McHutchison et al. (2010)	International/ (2007)	previously failed treated	342	Arm 1(T12PR24): Telaprevir/peg-interferon -2a/ribavirin for 12 weeks, followed by placebo/peg-interferon -2a/ribavirin for 12 weeks;	78 (68)	51 (22–65)	24 weeks
				Arm 2 (T24PR48): Telaprevir/peg-interferon -2a/ribavirin for 24 weeks, followed by peg-interferon -2a/ribavirin for 24 weeks;	80 (71)	52 (31–66)	48 weeks

Table 1: *Continued*

Reference	Setting/Year	Naïve/Previously Failed Treated	Total Sample Size (No.)	Arm	Male Sex–No (%)	Years of Age — Median (Range)	Total Treatment Duration
				Arm 3(PR48): Placebo/peg-interferon -2a/ribavirin for 24 weeks, followed by peg-interferon -2a/ribavirin for 24 weeks	76 (67)	50 (18–65)	48 weeks
				Arm 1(T12PR48): Telaprevir for 12 wk and peg- interferon/ribavirin for 48 wk;	183 (69)	51 (23–69)	48 weeks
				Arm 2(lead-in T12PR48): Peg-interferon/ribavirin for 4 wk, followed by telaprevir for 12 wk and peg-interferon and ribavirin up to a total of 48 wk;	189 (72)	51 (24–70)	48 weeks
Zeuzem et al. (2011)	International/ (2008–2010)	previously failed treated	662	Arm 3(PR48): Peg-interferon/ribavirin for 48 wk	88 (67)	50 (21–69)	48 weeks

all data from included trials to evaluate the effect of telaprevir. Therefore, subgroup analyses were conducted.

2.11.1. Subgroup analysis of telaprevir effect in naive patients

In naive patients, we found that telaprevir triple therapy presented a significantly higher rate of sustained virologic response than recommended PR48 regardless of T12PR24 (Odds Ratio (OR) 2.52; 95% CI 1.74 to 3.64), T12PR48 (Odds Ratio (OR) 2.89; 95% CI1.50 to 5.58), T12PR (Odds Ratio (OR) 3.78; 95% CI 2.76 to 5.19) or T8PR (Odds Ratio (OR) 2.82; 95% CI2.08 to 3.82), but not in T12PR12 (Odds Ratio (OR) 1.41; 95% CI 0.83 to 2.40) (Fig. 2). The rate of virologic response at the end of treatment was also significantly improved in T12PR12 (Odds Ratio (OR) 3.20; 95% CI 1.76 to 5.80), T12PR24 (Odds Ratio (OR) 1.88; 95% CI 1.24 to 2.87), T12PR48 (Odds Ratio (OR) 2.08; 95% CI 1.09 to 3.97), T12PR (Odds Ratio (OR) 3.69; 95% CI 2.55 to 5.34) and T8PR (Odds Ratio (OR) 2.46; 95% CI 1.76 to 3.46) (Fig. 3). In addition, telaprevir triple therapy also had a significant beneficial effect on the relapse rate in T12PR24 (Odds Ratio (OR) 0.34; 95% CI 0.14 to 0.82), T12PR48 (Odds Ratio (OR) 0.21; 95% CI 0.05 to 0.86), T12PR (Odds Ratio (OR) 0.24; 95% CI 0.15 to 0.40), T8PR (Odds Ratio (OR) 0.27; 95% CI 0.17 to 0.44), but not in T12PR12 (Odds Ratio (OR) 1.55; 95% CI 0.71 to 3.36) (Fig. 4).

As described in Table 3, 127 of 1191 (11%) and 48 of 581 (8%) naive patients suffered from severe adverse events in telaprevir-based groups and control groups, respectively. There was no significant difference between them (Odds Ratio (OR) 1.34, 95% CI0.94 to 1.90). 130 of 1028 (13%) naive patients in telaprevir-based groups discontinued the study treatment because of adverse events, as did 47 of 499 (9%) patients in the control group, there was no significant difference between them (Odds Ratio (OR) 1.33, 95% CI0.74 to 2.38). It also showed that telaprevir triple therapy significantly increased the risk of anemia, rash and pruritus both in naive patients, but it did not appear to increase the risk of neutropenia.

2.11.2. Subgroup analysis of telaprevir effect in patients previously treated unsuccessfully

In previously treated patients, telaprevir triple therapy had a significant effect on the rate of sustained virologic response in subgroups of T12PR24 (Odds Ratio (OR) 6.45; 95% CI 3.39 to 12.27), T24PR48 (Odds Ratio (OR) 6.93; 95% CI 3.64 to13.21), T12PR48 (Odds Ratio (OR) 9.00; 95% CI 5.34 to 15.17), and lead-in T12PR48 (Odds Ratio (OR) 9.83; 95% CI 5.82 to 16.60) (Fig. 5). The rate of virologic response at the end of treatment was also significantly improved in T12PR24 (Odds Ratio (OR) 7.31; 95% CI 4.07 to 13.12), and T24PR48 (Odds Ratio (OR) 4.83; 95% CI 2.76 to 8.47) (Fig. 6). In addition, telaprevir triple therapy significantly reduced relapse rate in T12PR24 (Odds Ratio (OR) 0.38; 95% CI 0.17 to 0.86), T24PR48 (Odds Ratio (OR) 0.13; 95% CI 0.05 to 0.35), T12PR48 (Odds Ratio (OR) 0.10; 95% CI 0.05 to 0.19), and lead-in T12PR48 (Odds Ratio (OR) 0.10; 95% CI 0.05 to 0.19) (Fig. 7).

As described in Table 3, 109 of 758 (14%) and 20 of 246 (8%) previously treated patients experienced severe adverse events in telaprevir-based groups and control groups, respectively. There was a significant difference between them (Odds Ratio (OR) 2.15, 95% CI1.29 to 3.58). 69 of 530 (13%) patients previously treated unsuccessfully in telaprevir-based groups discontinued the study treatment because of adverse events, as did 4 of 132 (3%) patients in the control group, there was a significant difference between them (Odds Ratio (OR) 4.79, 95% CI 1.72 to

Table 2: Methodological quality assessment of included trials

Reference	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Free of Source of Funding Bias?
Hèzode (2009)	Yes	Yes	Yes	No	Unclear	No
McHutchison (2009)	Unclear	Unclear	Yes	Yes	Unclear	No
Kumada (2011)	Unclear	Unclear	No	Unclear	Unclear	Yes
Jacobson (2011)	Unclear	Unclear	Yes	No	Yes	No
McHutchison (2010)	Unclear	Unclear	Yes	No	Unclear	No
Zeuzem (2011)	Yes	Yes	Yes	Yes	Yes	No

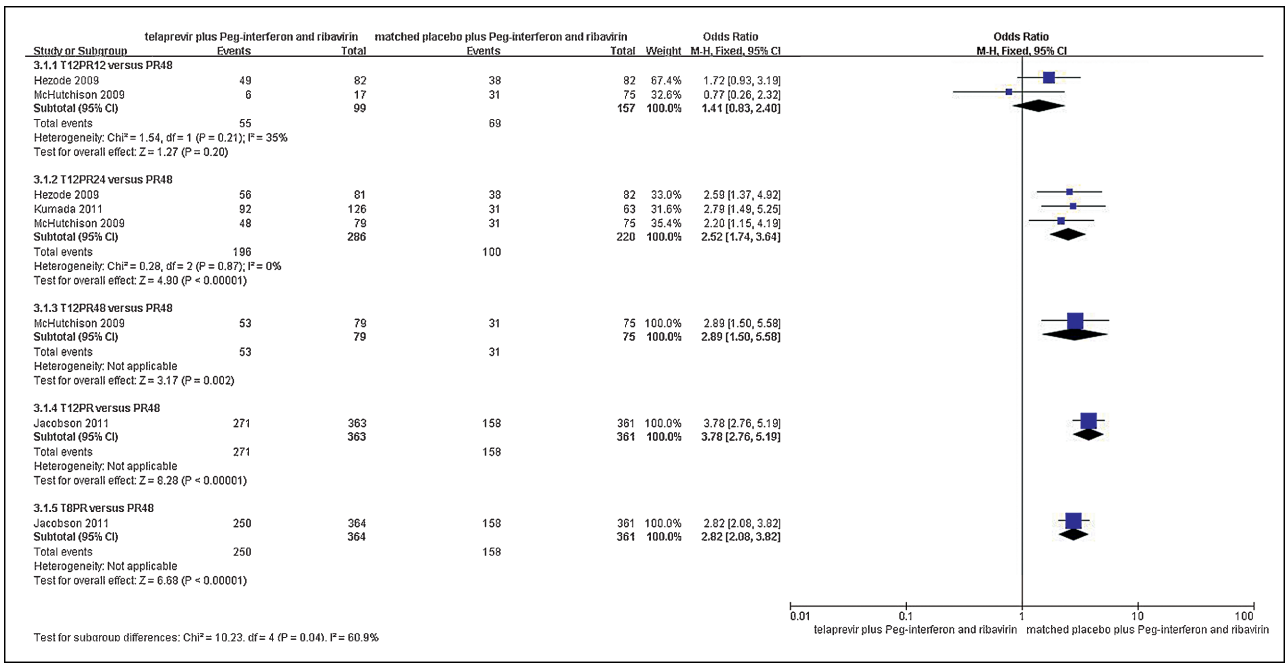

Fig. 2: Comparison of the proportion of naive patients achieving sustained virologic response in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

13.37). We also found that telaprevir triple therapy significantly increased the risk of anemia, rash and pruritus in previously treated patients, but the risk of neutropenia did not increase.

3. Discussion

Based on the result of this meta-analysis, we found that the combination therapy of telaprevir in combination with peginterferon alfa and ribavirin could not only significantly improve the rate of sustained virologic response and virologic response at the end of treatment but also reduce relapse rate in genotype-1-infected patients with chronic hepatitis C, except T12PR12 which seemed without improving sustained virologic response and decreasing relapse rate in naive patients. We also found that telaprevir triple therapy could increase the risk of severe adverse events and increase the rate of treatment discontinuation in previously treated patients but not in naive patients. Furthermore, it also increased the risk of commonly reported adverse events, such as: anemia, rash and pruritus, but seemed without increasing the risk of neutropenia.

The major limitations of this review are the low number of patients and the low methodological quality of the included trials. Most trials only mentioned randomization, but did not give adequate information so that we could not judge whether it was conducted properly. Only two trials (Hezode et al. 2009;

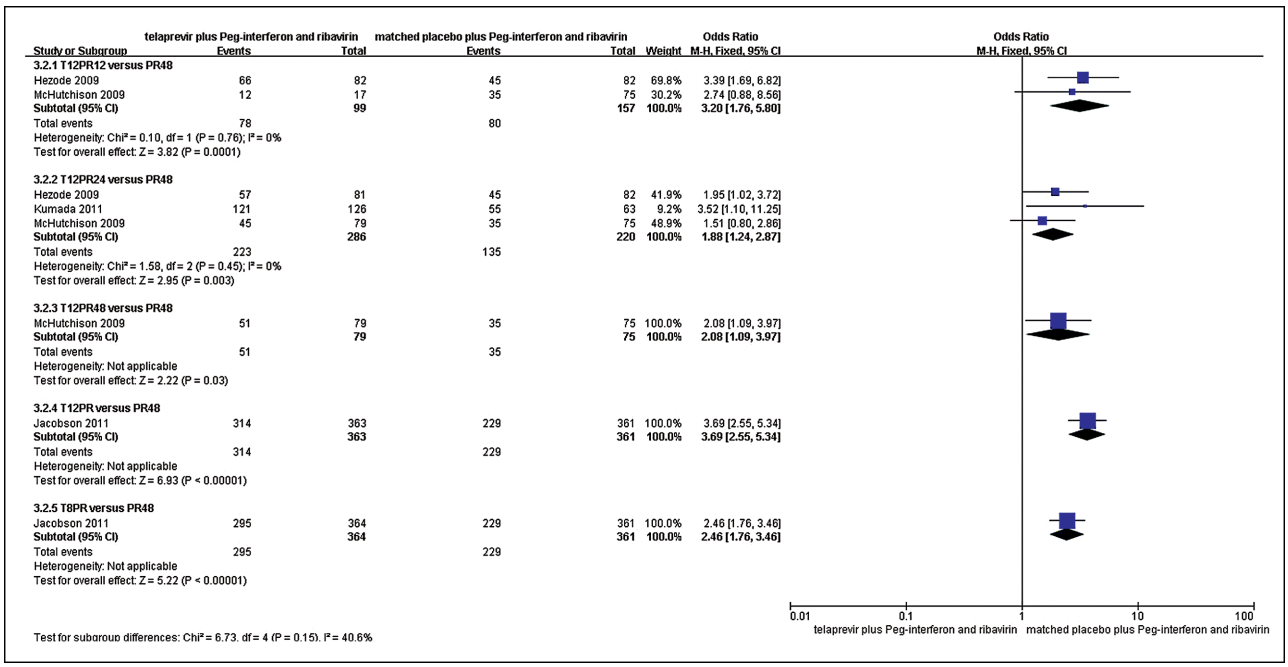

Fig. 3: Comparison of the proportion of naive patients achieving virologic response at the end of treatment in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

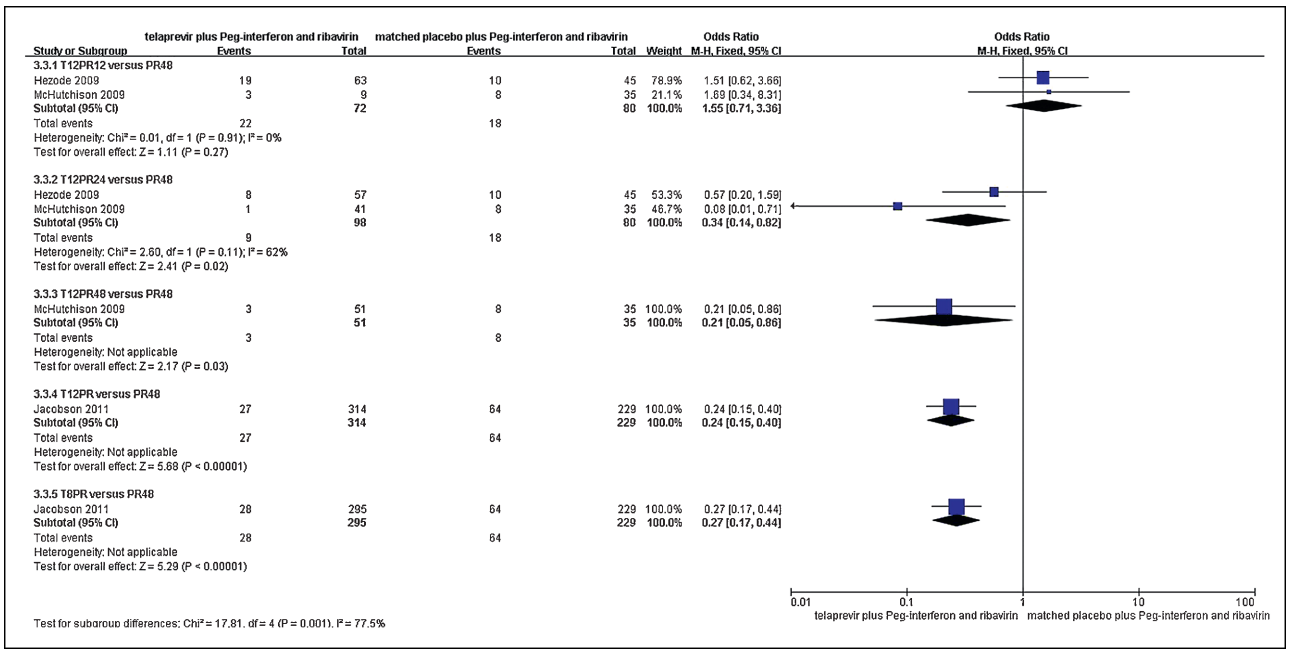

Fig. 4: Comparison of the proportion of naive patients relapsing to treatment in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

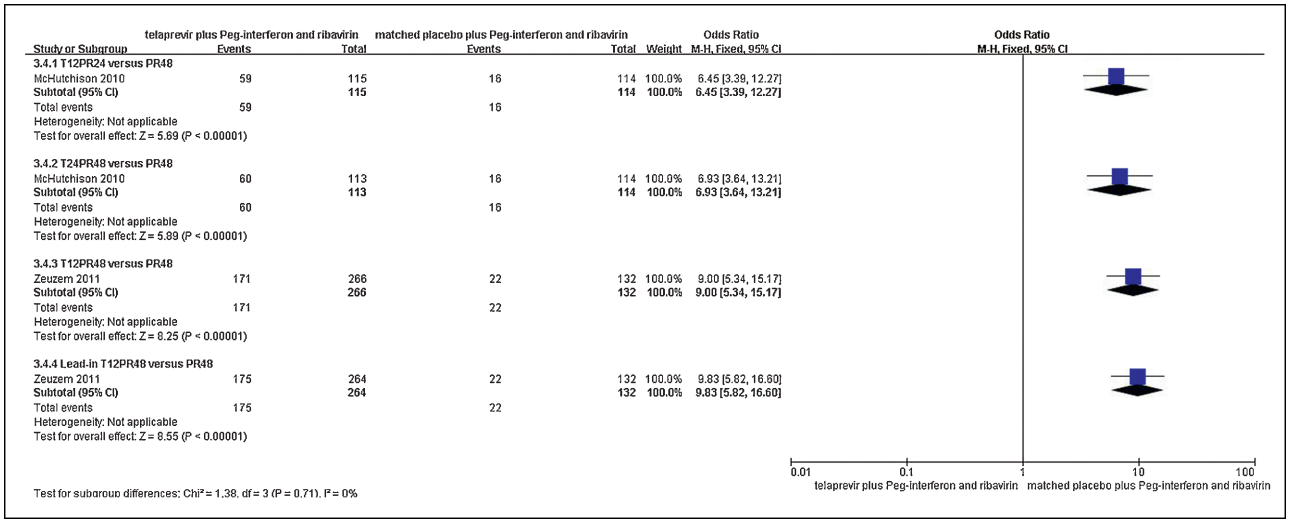

Fig. 5: Comparison of the proportion of previously failed treated patients achieving sustained virologic response in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin).

Zeuzem et al. 2011) reported adequate generation of the allocation sequence, only four trials (Jacobson et al. 2011; Kumada et al. 2012; McHutchison et al. 2009, 2010) reported adequate allocation concealment. In fact, only two trials (Hezode et al. 2009; Zeuzem et al. 2011) used both adequate randomization and blinding methods, which can guard against both selection and performance/outcome assessment biases. Only two trials (Jacobson et al. 2011; Zeuzem et al. 2011) protocol were available in order to assess selective outcome reporting. Five trials (Hezode et al. 2009; Jacobson et al. 2011; McHutchison et al. 2009, 2010; Zeuzem et al. 2011) were supported by pharmaceuticals companies.

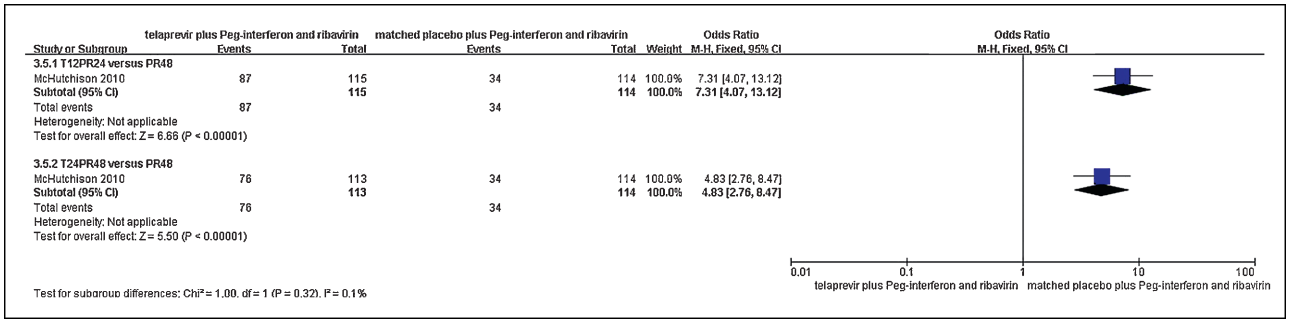

Fig. 6: Comparison of the proportion of previously failed treated patients achieving virologic response at the end of treatment in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

Table 3: Comparison of severe adverse events, treatment discontinuation, or commonly reported adverse events between the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

Trial	Intervention (Events/total)	Control (Events/total)	Statistical method	Effect estimate
Severe adverse events				
Naive patients				
Hèzode et al. (2009)	30/163	13/82	Odds Ratio (M-H,Fixed,95% CI)	1.34 [0.94,1.90]
Jacobson et al. (2011)	64/727	24/361		
Kumada et al. (2011)	15/126	7/63		
McHutchison et al. (2009)	18/175	4/75		
Previously failed treated patients				
McHutchison et al. (2010)	46/228	13/114	Odds Ratio (M-H,Fixed,95% CI)	2.15 [1.29,3.58]
Zeuzem et al. (2011)	63/530	7/132		
Treatment discontinuation				
Naive patients				
Jacobson et al. (2011)	72/727	25/361	Odds Ratio (M-H,Random,95% CI)	1.33 [0.74,2.38]
Kumada et al. (2011)	21/126	14/63		
McHutchison et al. (2009)	37/175	8/75		
Previously treated patients				
Zeuzem et al. (2011)	69/530	4/132	Odds Ratio (M-H,Fixed,95% CI)	4.79 [1.72, 13.37]
Commonly reported adverse events				
Anemia				
Naive patients				
Hèzode et al. (2009)	37/163	14/82	Odds Ratio (M-H,Fixed,95% CI)	2.43 [1.92, 3.08]
Jacobson et al. (2011)	276/727	70/361		
Kumada et al. (2011)	115/126	46/63		
McHutchison et al. (2009)	101/175	27/75		
Previously treated patients				
Zeuzem et al. (2011)	173/530	20/132	Odds Ratio (M-H,Fixed,95% CI)	3.14 [2.06, 4.77]
McHutchison et al. (2010)	60/228	9/114		
Neutropenia				
Naive patients				
McHutchison et al. (2009)	38/175	24/75	Odds Ratio (M-H,Fixed,95% CI)	0.59 [0.32, 1.08]
Previously treated patients				
Zeuzem et al. (2011)	73/530	14/132	Odds Ratio (M-H,Fixed,95% CI)	1.35 [0.73, 2.47]
Rash				
Naive patients				
Hèzode et al. (2009)	76/163	29/82	Odds Ratio (M-H,Random,95% CI)	2.65 [1.18, 5.95]
Jacobson et al. (2011)	262/727	88/361		
Kumada et al. (2011)	48/126	18/63		
McHutchison et al. (2009)	174/175	41/75		
Previously treated patients				
McHutchison et al. (2010)	126/228	23/114	Odds Ratio (M-H,Random,95% CI)	3.44 [1.76, 6.71]
Zeuzem et al. (2011)	194/530	25/132		
Pruritus				
Naive patients				
Hèzode et al. (2009)	93/163	29/82	Odds Ratio (M-H,Random,95% CI)	1.95 [1.15, 3.31]
Jacobson et al. (2011)	346/727	131/361		
Kumada et al. (2011)	23/126	13/63		
McHutchison et al. (2009)	112/175	23/75		
Previously treated patients				
McHutchison et al. (2010)	89/228	17/114	Odds Ratio (M-H,Fixed,95% CI)	3.06 [2.18, 4.29]
Zeuzem et al. (2011)	270/530	36/132		

In addition, several other factors may limit our results. Firstly, only 6 randomized controlled trials were included in the review. Secondly, one trial was tested in Japanese patients and the others in Netherlands, Germany, France, United States, Canada, Europe, America, Israel and Australia. Therefore, it is impossible to infer anything on the applicability of the drug in different populations. Thirdly, it may take many years for patients with hepatitis C to develop cirrhosis, hepatocellular carcinoma and eventually die (Alberti 1999; Brok et al. 2003). Therefore, a further weakness of the trials included in the present review is that our compiled data lack the long-term outcomes of intervention, such as liver histology, the incidence of end-stage liver disease or requirement for liver transplantation and liver-related mortality during follow-up period. However, no clinical trials assessing these outcomes have been carried out. Finally, using meta-analysis to analyze adverse events may have some bias. Although the total number of patients included in the systematic review seemed to be sufficient to underline the effect of telaprevir, more trials are required to further confirm its treatment efficacy and identify its adverse events.

We contacted the principal investigator of the trials to avoid including falsely randomized controlled trials. Because we could not search all databases for obtaining all relevant studies, potential bias may have taken place during the searching

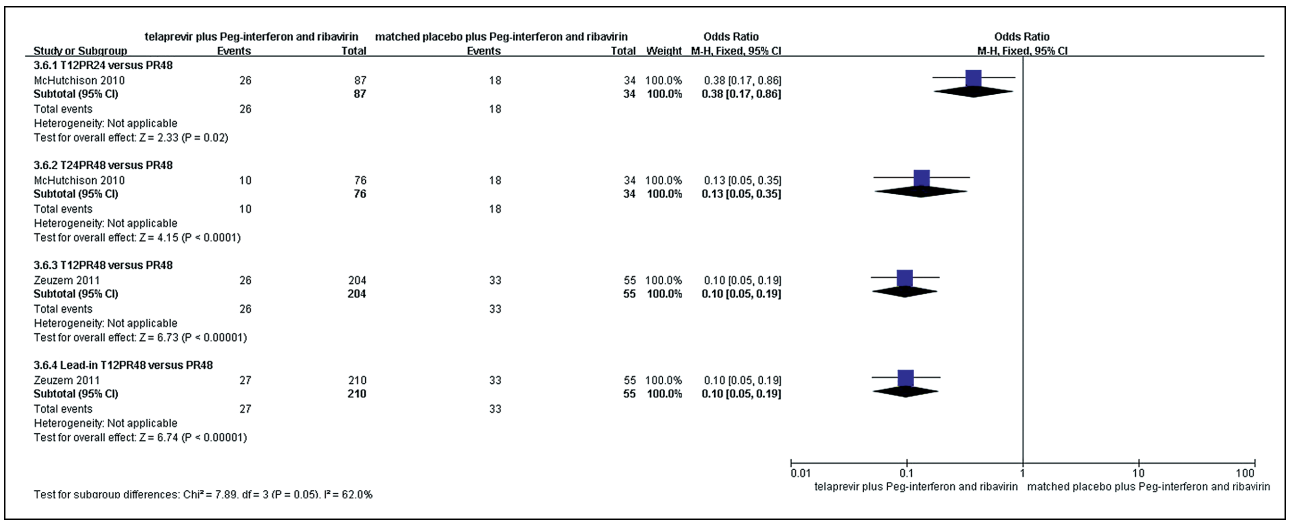

Fig. 7: Comparison of the proportion of previously failed treated patients relapsing to treatment in the trial intervention (telaprevir plus Peg-interferon and ribavirin) and the trial control (matched placebo plus Peg-interferon and ribavirin)

process. Owing to insufficient experience among systematic reviewers, there would be bias during the process of assessing methodological quality of the trials.

According to the meta-analysis result in the systematic review, we found that the combination therapy of telaprevir in combination with peginterferon alfa and ribavirin seemed to improve viral response in patients with genotype 1 chronic hepatitis C, which further confirmed the conclusion of the meta-analysis performed by Dang et al. (2012). Thus, telaprevir in combination with peginterferon alfa and ribavirin seems to be an effective therapy for naïve patients with genotype 1 chronic hepatitis C and those previously treated unsuccesfully. However, treatment should be monitored carefully as telaprevir triple therapy is associated with severe adverse events. Additional research is needed to evaluate the optimal dose and duration of treatment with telaprevir triple therapy. Long-term outcomes, such as liver histology, the incidence of end-stage liver disease or requirement for liver transplantation and liver-related mortality during longer follow-up, are needed to assess on the existing trials and research.

Conflict of interest statement:

We declare that we have no conflict of interest.

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