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Statin therapy improves response to interferon alfa and ribavirin in chronic hepatitis C: A systematic review and meta-analysis

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ABSTRACT

The treatment of interferon alfa (IFN-α) and ribavirin for chronic hepatitis C virus (HCV) infection achieves limited sustained virological response (SVR). We conducted a systematic review and meta-analysis to explore the efficacy of adding statins to IFN-α and ribavirin therapy for chronic hepatitis C. Studies with data pertinent to the effect of statins on chronic hepatitis C were reviewed, and randomized controlled trials (RCTs) evaluating the efficacy of the addition of statins to IFN-α and ribavirin were included in meta-analysis. The primary outcome measure was SVR. Secondary outcome measures were rapid virological response (RVR) and early virological response (EVR). The literature was systematically searched through October 2012. After screening of the 1724 non-duplicated entries, 54 potentially relevant studies were fully reviewed. Of those, 18 studies were relevant and 5 RCTs met the inclusion criteria for meta-analysis. In comparison with IFN-α and ribavirin therapy, the addition of statins significantly increased SVR (OR = 2.02, 95% CI: 1.38–2.94), RVR (OR = 3.51, 95% CI: 1.08–11.42) and EVR (OR = 1.89, 95% CI: 1.20–2.98). The SVR increase remained significant for HCV genotype 1 (OR = 2.11, 95% CI: 1.40–3.18). There were no significant increases in adverse events and withdrawals with the addition of statins. In conclusion, the addition of statins to IFN-α and ribavirin improves SVR, RVR, and EVR without additional adverse events and thus may be considered as adjuvant to IFN-α and ribavirin for chronic hepatitis C. Statins might also be used for HCV genotypes other than genotype 1, or in patients in whom the use of protease inhibitors is contraindicated or not indicated.

1. Introduction

It is estimated that 130 million to 170 million people are chronically infected with hepatitis C virus (HCV) worldwide (Lavanchy, 2009). Chronic hepatitis C, if untreated or treated ineffectively, may progress to liver cirrhosis and/or hepatocellular carcinoma (HCC) (Seeff, 2002). The treatment of chronic hepatitis C with pegylated interferon alfa (PEG-IFN-α) plus ribavirin, achieves a sustained virological response (SVR) rate of 40–50% in HCV genotype 1 infection administered for 48 weeks (Rosen, 2011). The introduction of direct acting antivirals (DAAs), such as telaprevir and boceprevir, in combination with PEG-IFN-α and ribavirin increases the SVR for genotype 1 infection (Butt and Kanwal, 2012). Therefore, the current standard of care (SOC) for chronic HCV genotype 1 is PEG-IFN-α, ribavirin and a DAA (protease inhibitor) (Ghany et al., 2011). However, drug resistance and side effects are important drawbacks of DAA treatment (Butt and Kanwal, 2012; Ghany et al., 2011; Vanwolleghem et al., 2007; Welsch and Zeuzem, 2012). The PEG-IFN-α and ribavirin therapy remains the SOC for HCV genotypes 2 and 3 disease with SVR of nearly 80%. However, there are still subgroups of difficult-to-cure patients with HCV genotypes 2 and 3 disease. Therefore, the efficacy of current therapy remains unsatisfactory and a novel strategy for improving SVR is required.

Host lipid metabolism plays an important role in HCV life cycle (Herker et al., 2010; Kapadia and Chisari, 2005; Maillard et al., 2011). HCV entry into hepatocytes involves the lipid metabolism (Owen et al., 2009). Cholesterol in particular has been implicated in HCV replication (Kapadia and Chisari, 2005; Monazahian et al., 1999). Moreover, the host-virus interaction may lead to metabolic disorders such as hepatic steatosis and insulin resistance (Negro, 2010; Ramalho, 2003), which are associated with reduced SVR rates (Adinolfi et al., 2011; Harrison et al., 2005; Thomopoulos et al., 2005). Statins, a class of drugs that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limit-

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ing enzyme of the cholesterol generation, are frequently used to lower blood cholesterol levels and are well known for their role in coronary and cerebrovascular events (Mihaylova et al., 2012). *In vitro* studies have shown that statins, especially fluvastatin, could effectively inhibit HCV RNA replication (Ikeda et al., 2006; Ye et al., 2003) and, when combined with interferon alfa (IFN-α), could enhance the anti-HCV effect of IFN-α (Ikeda et al., 2006).

Studies have investigated the role of statins in anti-HCV therapy in humans. For instance, two studies indicated that statins modestly reduced HCV RNA as monotherapy (Bader et al., 2008; Mihaila et al., 2009). A retrospective case-control trial using statins as monotherapy did not show a significant positive effect on HCV replication (Forde et al., 2009). Similar results were found in a pilot trial with atorvastatin (O'Leary et al., 2007) and a short-term (12 weeks) rosuvastatin monotherapy in non-responder HCV genotype 1 patients (Patel et al., 2011). In HCV-human immunodeficiency virus (HIV) coinfected patients, a pilot study showed that a 4-week fluvastatin monotherapy even increased rather than decreased HCV-RNA levels (Milazzo and Antinori, 2010; Milazzo et al., 2009). These studies indicate little or no antiviral effect of statins as monotherapy. However, fluvastatin, if combined with PEG-IFN-α and ribavirin, was shown to increase the SVR rates (Etani and Ida, 2011; Sezaki et al., 2009). In a retrospective case control trial, statin use was independently associated with SVR to PEG-IFN-α and ribavirin therapy after multivariate logistic regression (Harrison et al., 2010). In a propensity matched cohort, concomitant use of statin with PEG-IFN-α plus ribavirin resulted in a modestly increased SVR rates (Oni et al., 2012). In a prospective randomized study, the SVR rate was significantly higher in the fluvastatin combined with PEG-IFN-α plus ribavirin group than that in the non-fluvasatin group (Kondo et al., 2012). A controlled study showed that addition of fluvastatin to PEG-IFN-α and ribavirin significantly increased SVR and decreased viral load in relapse patients (Abd-Eldaem et al., 2012). In HIV/HCV genotype 1 coinfected patients, addition of fluvastatin to PEG-IFN-α and ribavirin therapy significantly improved the RVR, although it did not significantly increase the SVR rate (Milazzo et al., 2010). It is indicated that statins, if added to IFN-α and ribavirin treatment, may increase the virological response rates although some limitations such as the retrospective or non-control design and small number of patients included may compromise the validity of these studies. In order to clarify the efficacy and safety of statins in the anti-HCV therapy, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs).

2. Methods

2.1. Literature retrieval

We searched the following databases: Cochrane Library, PubMed, Web of Knowledge, Elsevier (ScienceDirect OnLine, SDOL), SpringerLink, and Wiley InterScience, to retrieve literatures investigating the effect of statins on HCV. The terms "hepatitis C", "hepatitis C virus or HCV", "viral liver disease", "3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor" and "statin" were used as search terms. Eligible trials were identified up to October 30, 2012 through electronic searches. For references of identified trials, hand-search was used.

2.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria were determined by two researchers (QZ and NL). Studies were considered for inclusion if they met the following criteria: (i) English language; (ii) the participants chronically infected with HCV; (iii) using statins; (iv) HCV RNA levels undertaken. For meta-analysis, the extra inclusion criterion was considered: virological responses, SVR, rapid virological response (RVR) or early virological response (EVR), measured. Studies were excluded if they were: (i) non English language; (ii) book sections, index, book or journal contents; (iii) irrelevant or relevant with other diseases; (iv) *in vitro* and animal studies; (v) with the participants co-infected with other viruses; (vi) pharmacokinetics studies; (vii) with patients younger than 16 years; (viii) in combination with other lipid modulators.

2.3. Data extraction and outcome measures

Data were extracted independently by two reviewers (QZ and NL) and validated by a third one (ZL). The following data were extracted: primary author, year, study design, numbers of patients and lost to follow-up, and dosage and duration of intervention. For the studies included in the meta-analysis, the first outcome measure was SVR rate. Secondary outcome measures included RVR and EVR. RVR was defined as the viral load of HCV undetected at the end of 4 weeks after therapy initiation. If the viral load was undetected at the end of the 12 weeks of therapy, this met the definition of EVR. After treatment completion, the patients were followed for 24 weeks and the cases negative for the virus at this time point were judged as SVR.

2.4. Methodological quality score of the included studies

The Jadad score was used to determine the quality of the RCTs (Jadad et al., 1996).

2.5. Data synthesis and statistical analysis

Meta-analysis was performed in Review Manager 5 (The Cochrane Collaboration, Oxford, England). Dichotomous variable data was presented as odds ratio (OR) with 95% confidence interval (CI). A Chi-squared test was used to assess the heterogeneity. I^2 value <25% was regarded as no heterogeneity. Fixed effects model was used when no significant heterogeneity existed among the studies analyzed. Mantel–Haenszel was used for the pooled effect. A P value <0.05 was considered to be significant. Adverse events and withdrawals were reported as a risk difference (RD, 95% CI).

3. Results

3.1. Search

The search strategy yielded a total of 1724 non-duplicated entries. After screening the titles, the type of entries and the abstracts, 54 articles were chosen for full review. A total of 18 studies were included for further reviewing. Of those, 6 were uncontrolled prospective trials and 7 were retrospective trials. The remaining 5 RCTs met the inclusion criteria for meta-analysis (Bader et al., 2012; Georgescu et al., 2011; Kondo et al., 2012; Malaguarnera et al., 2011; Shimada et al., 2012). The inclusion and exclusion process of the studies is shown in Fig. 1.

3.2. Characteristics of the included studies

The 5 studies for meta-analysis included 454 patients. Of the 454 patients, 441 were HCV genotype 1 and 13 were genotype 2 infection. The details of the characteristics of the 5 studies are shown in Table 1.

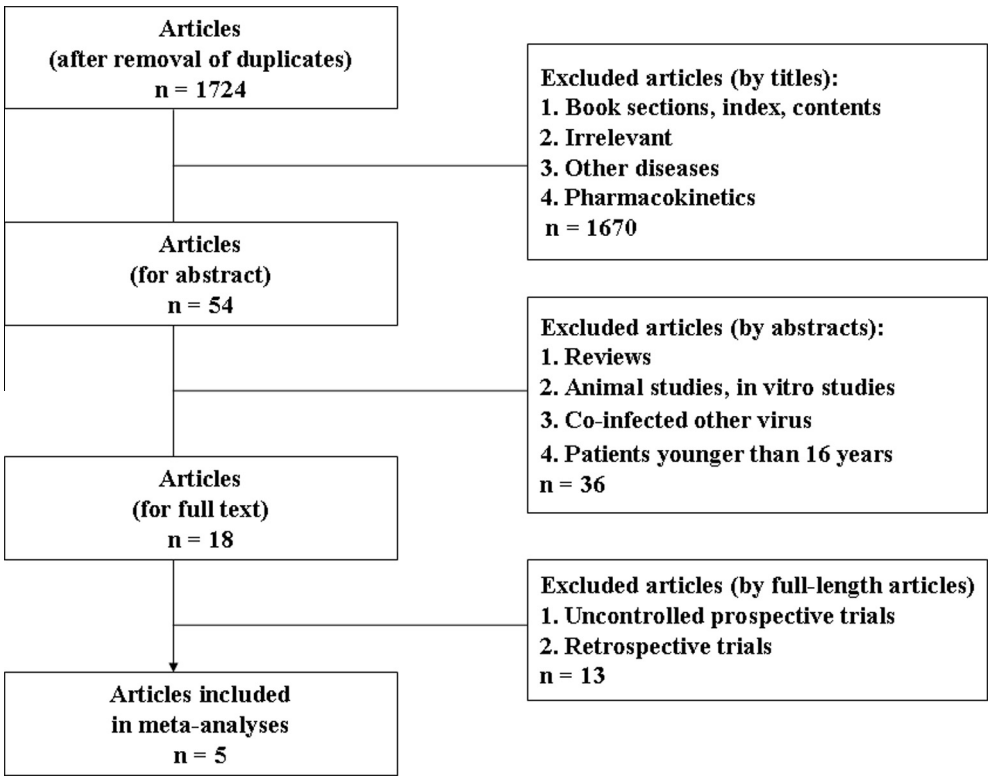

Fig. 1. Flow chart showing the inclusion and exclusion process of literatures.

Table 1
Characteristics of the randomized controlled trials included in meta-analysis.

Author, year	No. of patients (male)	HCV genotype (*n*)	Intervention	Control	Statin, dose	Duration (week)	Outcome
Bader et al. (2012)	44 (NA)	1 (44)	Fluvastatin + PEG-IFN-α + ribavirin or Simvasatin + PEG-IFN-α + ribavirin	PEG-IFN-α + ribavirin	Fluvastatin, 20 mg/d or Simvasatin, 10–80 mg/d	48	Addition of fluvastatin or simvasatin to PEG-IFN-α + ribavirin improved SVR
Georgescu et al. (2011)	209 (109)	1b (209)	Fluvastatin + PEG-IFN-α + ribavirin	PEG-IFN-α + ribavirin	Fluvastatin, 20 mg/d	48	Addition of fluvastatin to PEG-IFN-α + ribavirin improved EVR and SVR
Kondo et al. (2012)	94 (58)	1b (94)	Fluvastatin + PEG-IFN-α + ribavirin	PEG-IFN-α + ribavirin	Fluvastatin, 20 mg/d	48	Addition of fluvastatin to PEG-IFN-α + ribavirin improved SVR, but not RVR or EVR
Malaguarnera et al. (2011)	65 (38)	1 (52), 2 (13)	Rosuvastatin + IFN-α + ribavirin	IFN-α + ribavirin	Rosuvastatin, 5 mg/d	48	Addition of rosuvastatin to IFN-α + ribavirin did not improve SVR
Shimada et al. (2012)	42 (NA)	1b (42)	Pitavastatin + PEG-IFN-α + ribavirin	PEG-IFN-α + ribavirin	Pitavastatin, 1–2 mg/d	48	Addition of pitavastatin to PEG-IFN-α + ribavirin improved RVR and EVR, but not SVR

HCV, hepatitis C virus; NA, not available; IFN-α, interferon alfa; PEG-IFN-α, pegylated interferon alfa; SVR, sustained virological response; RVR, rapid virological response; EVR, early virological response.

3.3. Intervention

Therapeutic intervention regimens in the 5 studies included in meta-analysis are as follows: 2 studies used fluvastatin with PEG-IFN-α plus ribavirin as treatment (Georgescu et al., 2011; Kondo et al., 2012), 1 study used fluvastatin or simavastatin with PEG-IFN-α plus ribavirin as treatment (Bader et al., 2012), and 1 study used pitavastatin with PEG-IFN-α plus ribavirin as treatment (Shimada et al., 2012). All of these 4 studies used PEG-IFN-α plus ribavirin as control. The remaining 1 study used rosuvastatin with conventional IFN-α and ribavirin as treatment, and conventional IFN-α and ribavirin as control (Malaguarnera et al., 2011).

3.4. SVR

All of the 5 studies included in meta-analysis provided sufficient data for the pooled effect of SVR (Bader et al., 2012; Georgescu et al., 2011; Kondo et al., 2012; Malaguarnera et al., 2011; Shimada et al., 2012). In comparison with IFN-α and ribavirin dual anti-HCV therapy, statins increased the SVR rates when combined with IFN-α and ribavirin (OR = 2.02, 95% CI: 1.38–2.94). No significant heterogeneity was observed between these studies (I^2 = 0%, P = 0.80, Fig. 2). In order to exclude the possible confounding effect of non-genotype 1, sensitivity analysis was performed. The addition of statins to the dual combination therapy still significantly in-

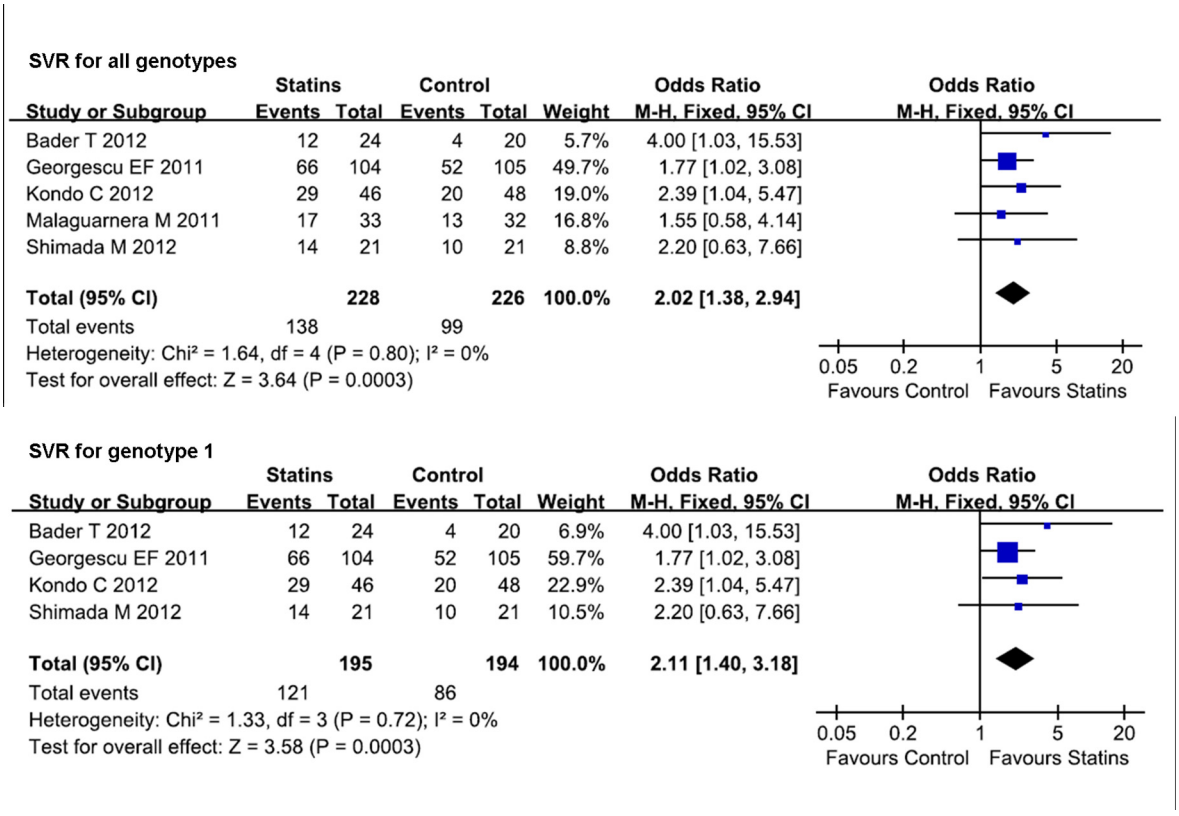

Fig. 2. Meta-analysis of sustained virological response (SVR) in all hepatitis C virus (HCV) genotypes and in HCV genotype 1. Odds Ratio and 95% confidence intervals (95% CI) for each study and the pooled estimate of the treatment effect with its 95% CI are plotted on the graph. Weight (%) represents the importance of each study relative to the overall analysis based on the number of patients. Studies are alphabetically arranged by author surnames.

creased the SVR rates compared with controls (OR = 2.11, 95% CI: 1.40–3.18). Heterogeneity was not significant (I^2 = 0%, P = 0.72, Fig. 2).

3.5. RVR

Two studies provided sufficient data for the calculation of pooled effect of RVR (Kondo et al., 2012; Shimada et al., 2012). Like the effect on SVR, statins obviously increased the RVR rates when combined with IFN-α and ribavirin in comparison with IFN-α and ribavirin controls (OR = 3.51, 95% CI: 1.08–11.42). There was no significant heterogeneity I^2 = 0%, P = 0.35, Fig. 3).

3.6. EVR

We calculated EVR from 3 studies with sufficient data (Georgescu et al., 2011; Kondo et al., 2012; Shimada et al., 2012). Compared to the controls, statins, in combination with IFN-α and ribavirin, also obviously increased the EVR rates (OR = 1.89, 95% CI: 1.20–2.98). No significant heterogeneity existed (I^2 = 23%, P = 0.27, Fig. 3).

3.7. Adverse events and withdrawals

There were no significantly increased adverse events noted in the combination with statins compared to the controls. According to World Health Organization, there were no serious adverse events reported in all of the 5 studies included in meta-analysis (Bader et al., 2012; Georgescu et al., 2011; Kondo et al., 2012; Malaguarnera et al., 2011; Shimada et al., 2012). Overall, there was no significant difference in withdrawals between the treatments with and without statins (RD = 0.01; 95% CI: −0.01–0.04, P = 0.36). No study had more than 10% loss to follow up. Details regarding adverse events and withdrawals are provided in Table 2.

4. Discussion

We performed a systematic review and meta-analysis of studies investigating the efficacy and safety of statins in combination with IFN-α and ribavirin in the anti-HCV therapy. Our analysis showed that statins, when combined with IFN-α and ribavirin, could augment the RVR, EVR and SVR rates in comparison with IFN-α and ribavirin dual therapy. Sensitivity analysis excluding the patients with non-genotype 1 HCV infection did not alter the effect of statins. No serious adverse events were reported in any of the five studies included in meta-analysis (Bader et al., 2012; Georgescu et al., 2011; Kondo et al., 2012; Malaguarnera et al., 2011; Shimada et al., 2012). Other studies also indicated that statins did not increase the risk of severe hepatotoxicity in chronic hepatitis C patients (Khorashadi et al., 2006; Lewis et al., 2007). Therefore, based on these findings revealing that statin use improves the effectiveness of IFN-α plus ribavirin without serious adverse events, statins may be added to the IFN-α and ribavirin dual anti-HCV therapy to increase SVR, especially for patients with HCV genotype 1 infection and contraindication with current protease inhibitors.

Several mechanisms of action of statins might be implicated in their beneficial role in the treatment of chronic hepatitis C, including host-targeting antiviral effects on the components required by HCV reproduction in intracellular lipid pathways and metabolic disorder-relieving and anti-inflammatory effects of the drugs. HCV assembly, maturation, degradation, and secretion are believed

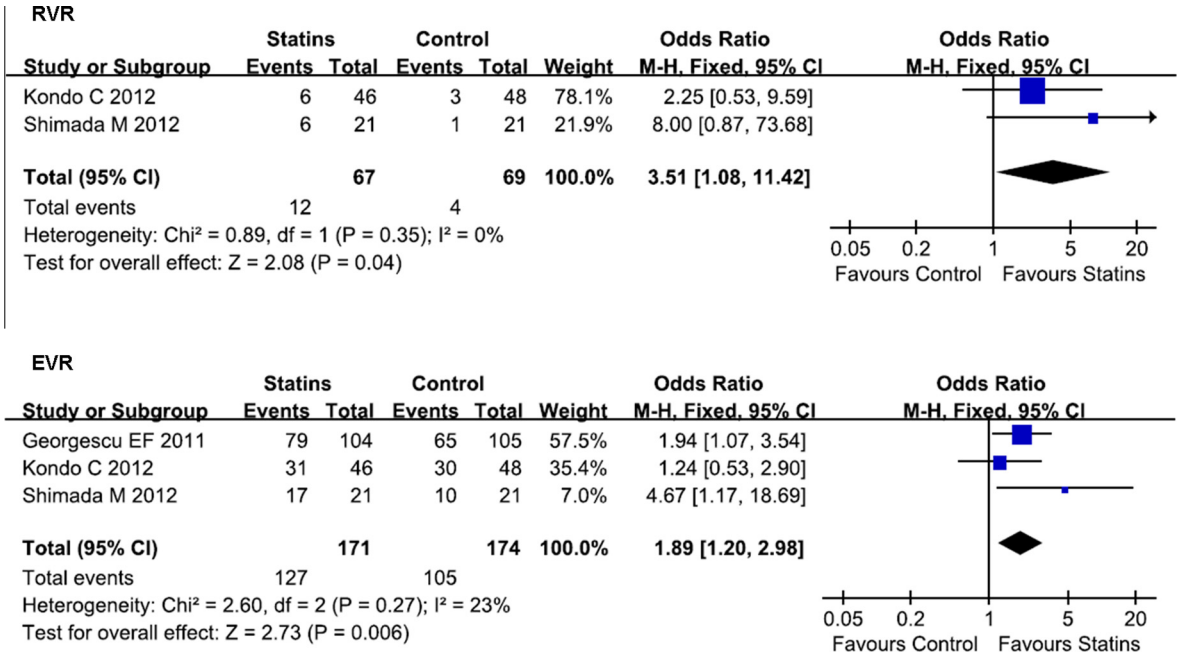

Fig. 3. Meta-analysis of rapid virological response (RVR) and early virological response (EVR). Odds Ratio and 95% confidence intervals (95% CI) for each study and the pooled estimate of the treatment effect with its 95% CI are plotted on the graph. Weight (%) represents the importance of each study relative to the overall analysis based on the number of patients. Studies are alphabetically arranged by author surnames.

to be associated with very low density lipoprotein (Gastaminza et al., 2008). It is indicated that the infectious HCV particles are lipoviroparticles (LVPs), which contain viral RNA, triglyceride, cholesterol, HCV core protein, apolipoprotein B and apolipoprotein E (Aizaki et al., 2008; Nielsen et al., 2006). Statins can inhibit the cholesterol synthesis by inhibiting the HMG-CoA reductase. It could also inhibit synthesis of geranylgeranyl pyrophosphate which binds to host protein and forms geranylgeranylated protein. Geranylgeranylated FBL2 was identified to promote HCV replication by direct binding to NS5A (Wang et al., 2005). Therefore, inhibition of the cholesterol and geranylgeranyl pyrophosphate synthesis may be relevant to the mechanisms of statins in suppressing HCV replication. Otherwise, improvement of the insulin resistance and reduction of the steatosis risk by statins may contribute to the enhanced SVR (Abdelmalek et al., 2010; Florentin et al., 2012; Malaguarnera et al., 2011). However, the only double-blinded randomized placebo-controlled trial failed to show any amelioration of the steatosis score by simvastatin assessed by repeat liver biopsy (Nelson et al., 2009) although atorvastatin significantly improved the steatosis grade and nonalcoholic fatty liver disease activity score assessed by liver imaging and histology in a subgroup of patients (Kimura et al., 2010). Hereof, further studies are needed to clarify the steatosis-improving role of statins in HCV treatment. Pro-inflammatory cytokines including interleukin-6 and transforming growth factor β1 were involved in the pathogenesis of chronic HCV infection (Grungreiff et al., 1999). The anti-inflammatory effect of statins (Jain and Ridker, 2005) may thus be one of the reasons leading to the enhanced anti-HCV effect. Increasing evidence from *in vitro* and animal studies showed that statins have a favorable effect on HCC via various mechanisms (Lonardo and Loria, 2012). Recently, a large population-based cohort study of 260,864 HCV-infected patients showed that statin use was associated with reduced risk of HCC (Tsan et al., 2013). Antiviral therapy with IFN-α and ribavirin reduces the incidence of HCC in chronic HCV infection (Masuzaki et al., 2010; Pearlman and Traub, 2011). A recent follow-up observation showed that combination of fluvastatin with PEG-IFN-α and ribavirin also reduces viral relapse in patients with HCV genotype 1b and high viral load (Atsukawa et al., 2013). It is therefore predictable that addition of statins to antiviral therapy for chronic HCV infection may further reduce HCC incidence.

It should be noted that statins may significantly interact with protease inhibitors, leading to exceedingly high statin concentrations and possibly increased adverse effects if used concomitantly. It is recommended that simvastatin, lovastatin and atorvastatin are contraindicated with telaprevir (Kiser et al., 2012; Lee et al., 2011). Simvastatin and lovastatin are also contraindicated with boceprevir (Seden and Back, 2011). When atorvastatin is coadministered with boceprevir, caution should be used, and an atorvastatin dose reduction and careful clinical monitoring are recommended (Seden and Back, 2011). In these cases, statins may be of interest in patients in whom the use of protease inhibitors is contraindicated

Table 2
Adverse events, withdrawals and quality analysis of the randomized controlled trials included in meta-analysis.

Author, year	Intervention group	Control group	Jadad score
Bader et al. (2012)	No withdrawals and safety issues	No withdrawals	2
Georgescu et al. (2011)	No report	No report	1
Kondo et al. (2012)	5 withdrawals: 1 for cytopenia, 2 for anorexia, 1 for malaise, 1 for depression	2 withdrawals due to cytopenia	3
Malaguarnera et al. (2011)	No withdrawals, adverse events: 2 with mild psychological disorders	No withdrawals, adverse events: 6 with mild psychological disorders	3
Shimada et al. (2012)	No withdrawals or safety issues	No withdrawals	2

or not indicated. Statins may also be of interest for HCV viral genotypes other than genotype 1 although we were unable to analyze the effect of statins on patients with these genotypes because of the small numbers of patients in the included studies. The potential of statins in difficult-to-cure HCV genotypes 2 and 3 patients also requires further evaluation. In addition, although addition of statin such as fluvastatin to PEG-IFN-α and ribavirin treatment has been shown to have no significant effect on serum cholesterol levels (Abd-Eldaem et al., 2012) and even preemptive statin usage has been revealed to be associated with higher SVR rates (Harrison et al., 2010), monitering of serum cholesterol levels should be recommended when statins are used given that untreated HCV infection *per se* may lower serum cholesterol levels in some patients.

The recent focus in anti-HCV therapy is mainly on the development of combination therapies containing different DAAs without interferon and/or ribavirin. However, low density lipoprotein cholesterol and statin use are still considered to be important associations of outcome with DAAs and the interactions of HCV and host lipid metabolism are still believed to play a relevant role in the era of DAAs for chronic hepatitis C (Sheridan et al., 2012). In view of this, statins may, at least in some respects, have an irreplaceable role in the successful treatment of chronic hepatitis C. Furthermore, *in vitro* studies have showed that statins increase the antiviral activity of different DAAs in an additive manner and delay or even prevent the development of resistance against DAAs (Delang et al., 2009). Future DAAs, including future protease inhibitors, may be compatible with statins. Hence, the combination of statins with DAAs may also have the potential to enhance the efficacy of DAAs and/or to prevent the development of resistance to DAAs in the future therapies without interferon and/or ribavirin.

Our analysis has some limitations. For example, the numbers of patients in the studies included were relatively small, the Jadad scores of the studies are low, and the unpublished studies with an estimated number of five (Gleser and Olkin, 1996) were not included in the analysis. These may lead to biases. In addition, we could not discriminate which statin was superior, since the statins used in the five studies were so different that no sufficient information may be used to perform sub-group analysis. In *in vitro* studies, different statins showed dissimilar inhibition of HCV replication, with fluvastatin being more effective and provastatin being less effective (Ikeda et al., 2006). We were unable to analyze whether the statin use increases the SVR rate in HCV genotypes 2 and 3 owing to the insufficiency of data. However, all of the studies included in meta-analysis provided sufficient data for calculation of pooled SVR effect and sensitivity analysis of the effect of statins on HCV genotype 1 infection, and the studies had no heterogeneity with I^2 value <25%, strengthening the validity of our analysis.

In conclusion, our study suggests that in comparison to dual anti-HCV therapy with IFN-α and ribavirin, the addition of statins to the dual therapy improves the SVR, RVR and EVR rates to chronic hepatitis C, including HCV genotype 1 infection, with no increased adverse events and withdrawals. Therefore, statins should be considered as an adjuvant to the IFN-α and ribavirin anti-HCV therapy to enhance the treatment response, especially for patients with HCV genotype 1 infection and/or contraindication with protease inhibitors. Statins might also be used for HCV viral genotypes other than genotype 1 or in patients in whom the use of protease inhibitors is not indicated. Statins in combination with inter-compatible DAAs may have the potential to enhance the efficacy of DAAs and/or to prevent the development of resistance to DAAs in the future therapies without interferon and/or ribavirin.

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