Clinics and Research in Hepatology and Gastroenterology (2017) xxx, xxx–xxx

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ORIGINAL ARTICLE

Statin use and virus-related cirrhosis: A systemic review and meta-analysis

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KEYWORDS
Statins;
Fibrosis;
Cirrhosis;
Decompensation

Summary
Background/objectives: Liver cirrhosis and its complications are important factors contributing to mortality worldwide. Statin use is probably associated with lower risk of hepatic decompensation and mortality, but not with cirrhosis or fibrosis progression according to a recent systematic review. We aimed to evaluate the definite effects of statins on the risk of virus-related cirrhosis.
Methods: We systematically searched four databases up to May 7, 2017, without language restriction. Studies were included if they evaluated and clearly defined exposure to statins, reported fibrosis progression, risk of cirrhosis in patients with chronic viral hepatitis or decompensation in cirrhotic patients, and reported relative risks (RRs) or odds ratios (ORs), or provided data for their estimation. Pooled RRs (or ORs) with 95% confidence intervals were calculated using the random-effects models irrespective of statistical heterogeneity assessed with the Cochran's Q statistic and I^2 statistic.
Results: Ten observational studies involving 12,3445 patients (8 cohort studies, $n = 12,1823$; 1 nested case-control, $n = 1350$; and 1 abstract, $n = 272$) were included. Statin use was associated with a statistically significant 51% reduction in the risk of virus-related cirrhosis (pooled RRs, 0.49; 95% CI, 0.30–0.80; $P = 0.004$), with substantial heterogeneity ($I^2 = 98.3\%$; $P < 0.001$). Statin use was also associated with a 51% reduction in the risk of decompensation (pooled RRs, 0.49; 95% CI, 0.41–0.59; $P < 0.001$), which was statistically significant, with no heterogeneity ($I^2 = 33.8\%$; $P = 0.210$).
Conclusions: The meta-analysis showed that statin use was associated with a significantly reduced risk of virus-related cirrhosis and decompensation. However, these results should be interpreted with caution given the possibility of residual confounding. Large randomized controlled trials are warranted in future studies.

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http://dx.doi.org/10.1016/j.clinre.2017.07.004
2210-7401/

Please cite this article in press as: Ma X, et al. Statin use and virus-related cirrhosis: A systemic review and meta-analysis. Clin Res Hepatol Gastroenterol (2017), http://dx.doi.org/10.1016/j.clinre.2017.07.004

Introduction

Liver cirrhosis and its complications are a worldwide public health problem. They contribute to mortality worldwide [1], accounting for more than 1 million deaths annually [2]. Liver cirrhosis is the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease [3]. Liver cirrhosis is generally speculated to be a consequence of wound healing response to chronic stimulation. Chronic infections with HBV and/or HCV are the major causes of cirrhosis, accounting for more than 50% of liver cirrhosis cases globally [4]. The process of virus-induced cirrhosis is a dynamic, multifaceted network. The predominant mechanism of virus-related liver cirrhosis is speculated to be an inflammation-necrosis-regeneration process caused by infections of active hepatic inflammation [5,6].

HBV is preventable or treatable, and HCV is now curable with existing treatments [7]. For virus-related liver cirrhosis and decompensation, elimination, prevention or reversal is a rare opportunity. But treatment of the underlying etiology may slow fibrosis progression. Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are used to treat and prevent coronary heart disease and stroke in patients with hyperlipidemia. In vitro and animal studies have shown that, in addition to cholesterol reduction, statins possess antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and anti-infective effects [8]. However, increasing evidence suggests that statins may be an effective preventative therapy for fibrosis progression [9] and virus-related liver cirrhosis in clinical studies [10,11]. According to a recent systematic review and meta-analysis by Kim et al. [12], statin use is probably associated with lower risk of hepatic decompensation and mortality. However, it is not associated with the risk of development of cirrhosis or fibrosis progression [risk ratio (RR), 0.42; 95% CI, 0.16—1.11] in adults with chronic liver diseases (CLDs) due to any cause. The systematic review had several limitations. First, it did not include case-control studies, and subgroup analysis was simple and based on the etiology of CLDs. Second, heterogeneity and publication bias were not analyzed in detail. A recent study assessing HCV patients randomized to long-term interferon use found that those on statins experienced decreased histological progression of fibrosis in multivariate models adjusted for several known predictors of fibrosis, but not in final/inclusive multivariable models [13]. This was likely related to the limited study power, given that only 29 subjects were taking statins and the majority of subjects had relatively advanced baseline liver disease (Ishak score of $\geq$ 3/6). Disagreements also exist about the antifibrotic effects of statins in other major organs. Some studies showed a protective effect of statins on cardiac and vascular fibrosis [14,15], whereas others showed no benefit or possible deleterious effect in persons with pulmonary fibrosis [16,17]. Given the concerns above, we performed a systematic review and meta-analysis of existing randomized controlled trials (RCTs) and observational studies (OSs) that investigated the association between statin use and the risk of developing virus-related liver cirrhosis.

Methods

Search strategy and selection criteria

We searched for clinical trials published until May 7, 2017 in PubMed, Ovid EMBASE, Web of Science, and Wiley Cochrane Central Register of Controlled Trials databases. The search string broadly included ''statin(s)'', ''HMG-CoA reductase inhibitor(s)'', ''atorvastatin'', ''fluvastatin'', ''lovastatin'', ''pravastatin'', ''rosuvastatin'', ''simvastatin''; and ''hepatitis B virus'', or ''hepatitis C virus''; and ''fibrosis'', ''cirrhosis'', ''decompensation'', Potential studies were searched and identified by X.S. M and C.S. L independently with conflicts adjudicated by a third reviewer (J.Y.). We contacted the authors to clarify the published data if necessary.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

- RCTs or OSs in adults (aged $\geq$ 18 years);
- comparison of fibrosis progression, the risk of cirrhosis in patients with chronic viral hepatitis (HBV or HCV) or decompensation in cirrhotic patients, between statin users and non-statin users.

The exclusion criteria were as follows: other study designs, such as quasi-experiments, unpublished studies, case reports, comments, editorials and letters. The study with the largest sample size or the latest publication was included if more than one study from the same team or institution met the inclusion criteria.

Data extraction and quality assessment

We selected studies and extracted data according to a standard Cochrane protocol. The following information was extracted in standardized forms: population characteristics, presence of diabetes, and Charlson comorbidity index. We also extracted data on trial characteristics (inclusion and exclusion criteria), type of study, statin intervention (type, dose, frequency), and medications that might affect the measured outcomes. Two investigators (X.S. M and C.S. L) independently reviewed the potential studies in terms of study characteristics and clinical relevance. Any disagreement between them was resolved by consulting the third investigator (J.Y.).

The quality of each OS was independently assessed by two authors (X.S. M and C.S. L) using the Newcastle-Ottawa scale (NOS), with the highest quality has nine stars. Studies with more than six stars are considered as high quality [18]. The Grading of Recommended Assessment, Development and Evaluation (GRADE) system [19], ranking as insufficient, low, moderate, or high, was used to evaluate the grading of the strength of evidence (SOE) for each outcome by two investigators (X.S. M and C.S. L) independently. Any discrepancy was resolved through a joint revaluation of the original article with the third author (J.Y.).

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