Statin efficacy in the treatment of hepatitis C genotype I

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INTRODUCTION

Hepatitis C virus (HCV) is an important human pathogen, not only because of its high prevalence and worldwide burden, but also because of the potentially serious complications of persistent HCV infection. These complications include cirrhosis, hepatocellular carcinoma, and end-stage liver disease necessitating liver transplantation. The incidence rates for all of these complications are expected to rise in the near future.[1,2]

It is estimated that 130-170 million people have chronic HCV (about 3% of the world population).[3,4] More than 3,000,000 people die every year from hepatitis C related liver diseases.[5] There is no vaccination for HCV, so the treatment is very important.

The standard medication of HCV (pegylated interferon (IFN) alpha plus ribavirin [RBV]) in HCV genotype I infected patients have shown 40-50% sustained virological response (SVR),[3] so we need more effective treatment method.

Lipid metabolism is one of the HCV life cycle steps. HCV forms a replication complex in lipid raft membrane that is full of cholesterol and sphingolipids.[6,7] 3-hydroxy-3-methyl-glutaryl Coenzyme A inhibitors (statins) can reduce cholesterol level and finally can decrease HCV replication. Hence, statin therapy can be introduced as a complementary treatment.

In vitro examinations have found that some statins, especially fluvastatin and atorvastatin can inhibit HCV replication,[8] although statins should be used with caution in advanced end-stage liver disease because of decompensation risk.[9]

Recently, beneficial effect of statin use among patients with HCV-related liver disease has been suggested. In vitro studies show that high concentrations of statins disrupt HCV replication through depletion of isoprenoid geranylgeranyl pyrophosphate.[10,11] Statins may thus have antiviral effects through mechanisms not related to lipid metabolism.[12,13] The low-density lipoprotein (LDL) receptor and the high-density lipoprotein scavenger receptor B1 putatively facilitate...
HCV entry into hepatocytes. Complex host proteins are found to be closely associated with HCV nonstructural proteins. The process which links these host and HCV proteins is termed prenylation. Statin agents which block the formation of the lipid precursors for prenylation, could theoretically interfere with viral replication.\textsuperscript{[14-16]}

Some human studies have done for assessing the effect of statins in hepatitis C treatment, but their results are different. O’Leary et al. have shown no reduction in HCV-ribonucleic acid (RNA) titers with 20 mg atorvastatin.\textsuperscript{[17]} However, another study indicates non-dose-dependent discretion in HCV-RNA in \%50 of patients,\textsuperscript{[18]} the purpose of this study was to determine the effect of statin therapy on standard antiviral treatment response in hyperlipidemic genotype I HCV patients.

**MATERIALS AND METHODS**

**Selection of patient groups**

Our study was a prospective clinical trial which was done on genotype I HCV patients who had been referred to educational and therapeutic centers of Isfahan University of Medical Sciences between years 2009 and 2010. All patients were tested to confirm HCV viremia by Cobas Amplicor HCV Monitor test, version 2 (Roche Diagnostics, Mannheim, Germany). We selected our patients using simple random sampling. Subjects in the statin group were hyperlipidemic patients according to WHO definition for hyperlipidemia which is LDL cholesterol level more than 160 mg/dl, 130 mg/dl for patient with one risk factor and 100 mg/dl for patients with diabetes mellitus, 2 or more than risk factors. Patients in the placebo group were selected from HCV patients without hyperlipidemia. This study protocol was approved by Institutional Review Board and Ethics Committee of Isfahan University of Medical Sciences (research project number: 309079).

Patients were included in the study if they were naïve for HCV treatment, more than 18 years old and patients who did not have any clinical sign for decompensate Cirrhosis. All cases who were affected by other genotypes of HCV and chronic liver disease such as hepatitis B virus, HIV, Wilson disease, hemochromatosis, autoimmune liver disease, primary biliary cirrhosis, secondary biliary cirrhosis, obstructive liver disease, viral infections that affect liver function, and who had the history of alcohol drinking and drugs related steatosis and hepatotoxicity were excluded from our study. Patients were excluded from the study if the level of their liver enzymes (alanine transaminase and aspartate aminotransferase) had risen >3 times during statin treatment. Patients were examined clinically before antiviral treatment. Fasting blood sugar, plasma lipids, liver enzymes tests and liver and abdomen sonography (Hitachi, Tokyo Japan) were done 2 times (with 1 month apart) before treatment for all of them. We also checked their blood pressure, waist size, and body mass index (BMI) according to related guideline.\textsuperscript{[19]} All patients weekly received 180 μg Peg-IFN-a2a and 1000, 1200 and 1400 mg RBV for weights <75 kg, 75-100 kg, and more than 100 kg, respectively (Pegasys Co.). Statin group received 20 mg atorvastatin (Farabi Co., Tehran, Iran) nightly for 3 months and placebo was prescribed for the placebo group the same as atorvastatin in the statin group. Liver enzymes and complete blood count were checked monthly and thyroid stimulating hormone checked every 3 months. We also did quantitative HCV-RNA test to reveal patients with undetectable test in 12th week of therapy (early virological response [EVR]), after therapy (end of treatment virological response) and 6 months after therapy SVR for all samples.

We analyzed our data using SPSS version 16 (Inc., Chicago, IL, USA) and considered \( P < 0.05 \) as valuable, Chi-square was applied for comparison of categorical parameters and Student’s \( t \)-test for comparing the continuous parameters.

**RESULT**

Our study included 40 HCV positive patients (20 hyperlipidemic and 20 normolipidemic patients). Our results showed that there are significant differences in the mean of BMI, triglyceride, LDL, and cholesterol between statin and placebo groups [Table 1].

The evaluation of viral load before statin therapy did not show any significant difference between statin and placebo, also, we didn’t find any significant differences in the mean of HCV-RNA numbers in statin and placebo groups in 12th week of Statins therapy (\( P > 0.05 \)), at the end of treatment (\( P > 0.05 \)) and 6 months after treatment (\( P > 0.05 \)) [Table 2]. Our findings also implied that EVR in statin and placebo were 75 and 70% and SVR was 95% in both groups. ALT level was higher in statin group before treatment [Table 3]. Although both AST and ALT level rose after treatment, we did not find any difference between AST and ALT level after treatment.

**Table 1: demographic and lipid character in statin and placebo group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statin group</th>
<th>Placebo group</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±5.9</td>
<td>20.6±3</td>
<td>0.04</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>249±17.6</td>
<td>206±24.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>306.9±71.6</td>
<td>168.5±32.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>45.9±11.5</td>
<td>42.3±7.9</td>
<td>0.35</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>189.5±13.7</td>
<td>129±20.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>18/2</td>
<td>17/3</td>
<td>0.36</td>
</tr>
<tr>
<td>Age (year)</td>
<td>32±10</td>
<td>34.9±9.8</td>
<td>0.36</td>
</tr>
</tbody>
</table>

BMI = Body mass index; TG = Triglyceride; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; SD = Standard deviation
inhibiting HCV RNA replication. Furthermore, a 
nonrandomized comparative study of 31 patients 
with chronic hepatitis C and hypercholesterolemia 
who were given atorvastatin showed a decrease in 
HCV-RNA replication compared to baseline.

A pilot study of 31 HCV-infected veterans who 
were given lovastatin 20-320 mg/day for 2-12 weeks 
with weekly monitoring of HCV-RNA and liver 
tests reported modest reductions of viral load. 
Furthermore, a pharmacoepidemiologic study found 
that the use of lovastatin was associated with a 
40-50% lower incidence of moderate as well as severe 
liver injury among patients with preexisting liver disease.

Even though, prior individual studies examined 
important aspects of the association between statin 
and lowering the severity if liver disease in HCV-infected 
patients, these studies either did not adjust for histological 
severity of liver disease, had generally short follow-up, or 
did not use placebo subjects. Clearly, more information 
is needed about the possible beneficial effect of statins in 
HCV-infected.

The result of other in vivo studies has been same as our 
findings in this study. A study which has done by O’Leary et al. (2007) on 10 samples show that atorvastatin does not 
inhibit HCV-RNA replication in vivo. Forde et al. in a 
cross-sectional study (2009) confirmed that statins don’t have any apparent effect on HCV-RNA replication in vivo.

Unlike in vivo studies the result of in vitro research has shown 
that statins can decrease HCV-RNA replication. Ikeda et al. 
evaluated the effect of statins on HCV-RNA replication in 
OR6 cells. Fluvastatin exhibited the strongest anti-HCV 
activity while atorvastatin and simvastatin showed 
moderate inhibitory effects. The combination of IFN and 
the statins showed strong inhibitory effects on HCV-RNA 
replication.

There are some reasons for differences between in vitro and 
in vivo studies. As we told before various factors affect on 
antiviral treatment response in the human body such as 
severity of liver disease, had generally short follow-up, or 
did not use placebo subjects. Clearly, more information 
is needed about the possible beneficial effect of statins in 
HCV-infected.

In summary in our study statins did not have any signi 

cant effect on HCV-RNA replication. Our 

discovery is in agreement with the results of a 

randomized controlled trial (RCT) conducted by 

Weiss et al. (2006) which showed that 

lovastatin was associated with a modest decrease in 

HCV-RNA replication.

In our study, response rate of patients were higher than 
western studies, there are some similar reports that show 
high response rate of combination therapy in Iranian 
patients, it may be due to lower viral load in comparison 
to western patients.

In summary in our study statins did not have any significant 
effect on HCV virus number and virologic response. Our 
limitation in this study was few sample size, and further 
studies are necessary to examine the possible antiviral 
properties of statins and their potential role as adjuncts to 
standard HCV therapy.

AUTHORS’ CONTRIBUTION

All authors have contributed in designing and conducting the 
study. Ash, AB, SS, Sh, and Nkh collected the data and MM, 
MKh, MT, Ash, and BA did the analysis. All authors have 
assisted in preparation of the first draft of the manuscript 
or revising it critically for important intellectual content. 
All authors have read and approved the content of the 
manuscript and are accountable for all aspects of the work.

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