The Pleiotropic Effects and Therapeutic Potential of the Hydroxy-Methyl-Glutaryl-CoA Reductase Inhibitors in Gastrointestinal Tract Disorders: A Comprehensive Review

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INTRODUCTION

Statins, through the inhibition of the hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase, have been the main treatment for dyslipidemia, and for the primary and secondary prevention of coronary artery disease[1]. However, statins are increasingly being recognized as possible preventative or therapeutic agents in a wide range of other disorders, including heart failure, cardiac arrhythmias, chronic obstructive lung disease, cancer, connective tissue disorders, dementia, and infectious diseases, through other mechanisms not associated with the lipid lowering effects [2-4]. These non-lipid lowering properties, also known as pleiotropic effects, are believed to be due to the inhibition of isoprenoid synthesis, which leads to decreased levels of C reactive protein, suggesting that statins may have anti-inflammatory properties [2, 5]. Data suggests that the use of statins in patients with gastrointestinal pathologies such as non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease, cholelithiasis, hepatitis, and malignancies among others, may have multiple favorable effects, regardless of their cholesterol level or cardiovascular health status [6]. We conducted a comprehensive review of existing literature regarding the pleiotropic effects of statins in gastrointestinal disorders.

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is a common cause of elevation of the liver enzymes, and encompasses a spectrum of disorders ranging from hepatic steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. Because a strong association with other comorbidities such as obesity, diabetes mellitus, and hyperlipidemia, patients with NAFLD have a greater risk of mortality from cardiovascular disease [7]. However, the use of statins in patients with NAFLD has been limited out of concern of their possible hepatotoxicity.

The use of pravastatin was evaluated in patients with NASH for six months in five patients with elevated baseline liver enzymes. Liver histology improved after treatment, demonstrating improvement in the degree of inflammation and steatosis, without a significant elevation of the liver enzymes [8]. Similar results were observed in a study where a liver biopsy was taken in 19 patients with dyslipidemia. Clinical
and histological alterations were evaluated before and after treatment with rosuvastatin during 24 months. NAFLD activity score and fibrotic stage improved in one third of the patients, with only one out of nine patients demonstrating progression of the liver fibrosis [9].

The GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study was a prospective, randomized study, which analyzed the risk reduction for the first recurrent cardiovascular event in patients treated with statins (mainly atorvastatin) [10]. A post-hoc analysis of this study evaluated the effect of statins therapy in a group of patients who had moderately abnormal liver enzymes (defined as serum liver enzymes concentrations of less than three times the upper limit of normal [ULN]) and compared them with a similar group of patients that did not receive statins. Of 437 patients with moderately abnormal liver tests at baseline, 227 in the statins group had a substantial improvement in the liver enzyme levels, whereas 210 patients not treated with statins had further increases of their liver enzyme concentrations (p<0.0001) [11].

Statins have also been demonstrated to reduce tumor necrosis factor alpha, interleukin-6, and possibly C reactive protein, all of which are known markers of inflammation in advanced NASH [12]. These findings suggest that statins may be beneficial and could be safely used in patients with NAFLD/NASH and cirrhosis [13].

**INFLAMMATORY BOWEL DISEASE**

Patients with inflammatory bowel disease (IBD) are at an increased risk for atherosclerosis, possibly through a pro-inflammatory state, elevated homocysteine levels, and insulin resistance [14]. Statins have been shown to reduce the expression of chemokines and inflammation, which have been shown to be of benefit for patients with IBD [15]. A retrospective study of 1,986 patients with IBD showed an 18% reduction in the rate of steroid initiation in patients treated with statins (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.71-0.94) [15]. However, the significance was only observed with atorvastatin (HR 0.76, 95% CI 0.6-0.96) and in patients with ulcerative colitis (HR 0.75; 95% CI 0.62-0.91) [15].

Atorvastatin also reduced plasma CXCL10 chemokine levels in a study of 10 patients with Crohn's disease after 13 months of treatment, which resulted in a reduction in the amount of low density lipoprotein cholesterol oxidation and inhibition of monocyte migration to inflamed tissue, thereby attenuating the inflammatory response [15, 16].

Persistent inflammation of the colon mucosa may lead to aneuploidy, loss of heterozygosity, and p53 mutations, therefore patients with IBD have an increased risk for the development of colorectal cancer (CRC) [17]. A case-control study of 1,921 patients demonstrated that the use of statins was associated with a reduced risk of IBD-associated CRC (OR 0.07; 95% CI, 0.01-0.78) [17]. However, after adjustment for potential confounders, there was only a trend towards the risk reduction (OR 0.1, 95% CI 0.01-1.31; p=0.08), and a subgroup analysis showed that only simvastatin was associated with a significant risk reduction of IBD-associated CRC (OR= 0.05; 95% CI, 0.004-0.54; p=0.014) compared with non-statin users.

**GASTROINTESTINAL MALIGNANCIES**

Data suggests that simvastatin exerts anti-proliferative, pro-apoptotic, and anti-invasive effects in cancer cells [18, 19]. Statins may oppose CRC growth by inducing apoptosis, through a down-regulation of anti-apoptotic proteins such as BCL2 or CIAP1, and an up-regulation of pro-apoptotic proteins such as bone morphogenetic protein. A study where cell lines with CRC were treated with simvastatin showed an induction of apoptosis in a dose and time-dependent manner, through down-regulation of those anti-apoptotic proteins [20]. Also, it has been suggested that high dose statin inhibits angiogenesis based on the presence of promoters, such as hypoxia through the inhibition of vascular endothelial factor, or tumor necrosis factor [20, 21]. Statins may also limit the ability of tumor cells to metastasize through the inhibition of Rho-regulated expression of E-selectin by tumor necrosis factor, as well as the modulation of an inflammatory response [22]. This was confirmed in a retrospective case-control study of male patients with new diagnosis of CRC which showed a 30% reduction in the prevalence of metastasis in patients with CRC who were taking statins, compared with non-users (OR 0.7, 95% CI 0.4-0.9; p<0.01) [23].

Despite the benefits of statins in cancer cells observed in the studies mentioned above, a meta-analysis observed only a trend towards protection against the incidence of CRC with statins (RR 0.94, 95% CI 0.86-1.04) [24]. Another meta-analysis of three large colorectal adenoma chemoprevention trials showed that statin therapy was not associated with a reduced incidence of adenomas (relative risk [RR] 1.03, 95% CI 0.87-1.23), advanced adenomas (RR 1.13, 95% CI 0.70-1.81), or multiple adenomas (RR 1.25, 95% CI 0.95-1.65) [25].

In hepatocellular carcinoma, similar observations regarding statins and their role in prevention, or as adjuvant therapy, have been made. A recent study evaluated the effects of simvastatin on tumor cell growth, apoptosis, and cell cycle in cell cultures of hepatocellular carcinoma. It was observed that in cell lines pretreated with simvastatin for 48 hours there was significant induction of apoptosis and arrest of the cell cycle, and therefore a slower cell growth was demonstrated when compared with control cells, p<0.05. It was also shown that the longer the exposure to simvastatin (pre-treatment of 48 or 72 hours), the slower the cell growth [26]. Another study, assessing the use of statins for more than 2 years in diabetic patients, showed that having a prescription for any statin was associated with a reduced risk of developing hepatocellular carcinoma [27].

The benefit of statins has also been demonstrated in patients with Barrett's esophagus, and esophageal carcinoma. Ogunwobi et al [28] evaluated the effects of statins on Barrett's esophagus cells and showed that there is inhibition of the proliferation and induction of apoptosis, resulting in a reduction of viable cancer cells, showing a potential chemopreventative and adjuvant chemotherapeutic agent in this type of cancer. In another study, of 411 patients with Barrett's esophagus, the association between statins use and the progression to esophageal adenocarcinoma was assessed through endoscopic surveillance one year after starting statins [29]. It was observed that the use of statins reduced the development of Barrett's esophagus (HR 0.68; 95% CI, 0.30-1.54). Similar results were obtained in a
multicenter study where 570 patients with Barrett’s esophagus were followed for a median of 4.5 years and the use of statins was associated with a significantly reduced risk of neoplastic progression (HR 0.46, p=0.048) [30].

Different adverse prognostic indicators have been described in esophageal cancer such as the expression of intracellular adhesion molecule-1 (ICAM-1), and contribute to its metastatic potential. Statins were evaluated in their ability to attenuate tumor growth and malignant potential of esophageal cancer cells in vitro, and it was demonstrated that simvastatin attenuates the cell-surface ICAM-1 expression, decreasing cell viability and increasing apoptosis [31]. A review of experimental and epidemiological evidence of statins and the risk of esophageal cancer strongly suggested that statins inhibit proliferation, induce apoptosis, and may limit metastatic potential in esophageal cell lines [32].

The effects of statins on pancreatic cancer have also been evaluated. A meta-analysis of 16 studies, with a total of 1,692,863 participants, indicated a non-significant decrease of pancreatic cancer risk among all statin users (RR 0.89; 95% CI 0.74-1.07) [33].

VIRAL HEPATITIS

In vitro data suggests that statins may inhibit hepatitis C virus (HCV) replication [34]. The underlying mechanism remains unclear, but it has been hypothesized that the HCV requires elements of the cholesterol and fatty acid biosynthetic pathways to enter the hepatocyte via lipoprotein receptors [35]. It also has been shown that very low density lipoprotein particles attach with HCV virions in human serum [35]. Delang et al showed that statins inhibit the replication of subgenomic HCV-1b replicons and suppress RNA replication of fulminant hepatitis-1 HCV [36]. Different types of statins and their anti-HCV activity were tested in vitro, and mevastatin, simvastatin, lovastatin and fluvastatin inhibited HCV replication in a dose-dependent manner. Mevastatin and simvastatin showed the strongest anti-HCV activity, but fluvastatin and lovastatin had moderate inhibitory effects. The combination of mevastatin plus interferon alfa, or with selective HCV polymerase and protease inhibitors had an additive effect on viral replication, which is necessary to delay or prevent the development of viral escape mutants [36, 37].

A multicenter study of patients with chronic HCV, found a significantly higher sustained virological response rate among patients who were receiving statins prior to antiviral therapy versus those not using statins, 53% versus 39.3%, respectively (p=0.02) [38]. The virological response rates were significantly higher at 4 and 12 weeks after statin therapy. The relapse rates were 16.7% amongst the statin users versus 25.8% in the non-statin users.

The safety and effectiveness of chronic statin therapy in patients with HCV was evaluated in a follow-up study of 22 months [39]. A reduction of 22% in the low-density lipoprotein levels was noted (p<0.01). The authors concluded that in patients without significantly elevated baseline liver enzymes, statin therapy may be considered when clinically indicated and appears to be safe in these patients.

The evidence of statins for the treatment of hepatitis B virus (HBV) infection is modest. It has been reported that simvastatin exhibits strong in vitro anti-HBV activity, and when it is used in combination with any nucleoside analogue (lamivudine, Table I. The reported benefits of statin therapy in gastrointestinal disorders.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis/cirrhosis</th>
<th>Inflammatory bowel disease</th>
<th>Colorectal cancer</th>
<th>Hepatocellular carcinoma</th>
<th>Viral hepatitis (hepatitis C and B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve liver pathology</td>
<td>Decrease degree of inflammation</td>
<td>Decrease use of steroids</td>
<td>Anti-proliferative, pro-apoptotic and anti-invasive effects in cancer cells</td>
<td>Anti-proliferative, pro-apoptotic and anti-invasive effects in cancer cells</td>
<td>May inhibit viral replication</td>
</tr>
<tr>
<td>Decrease TNF-α, IL-6, CRP</td>
<td>Safe use, no increase in liver enzymes</td>
<td>Attenuate inflammatory response</td>
<td>Impair angiogenesis in tumor cells</td>
<td>Reduce the risk of hepatocellular carcinoma in prior known liver disease patients</td>
<td>Increase sustained virological response</td>
</tr>
<tr>
<td>Safe use, no increase in liver enzymes</td>
<td></td>
<td>Decrease the risk of progression to colorectal cancer</td>
<td>Decrease the ability to metastasize</td>
<td></td>
<td>Additive effect with IFN-α or anti-retrovirals</td>
</tr>
<tr>
<td>Decrease degree of inflammation</td>
<td></td>
<td>Reduce the risk of hepatocellular carcinoma in prior known liver disease patients</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Decrease TNF-α, IL-6, CRP</td>
<td></td>
<td>May inhibit viral replication</td>
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<td></td>
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<tr>
<td>Decrease TNF-α, IL-6, CRP</td>
<td></td>
<td>Increase sustained virological response</td>
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<tr>
<td>Safe use, no increase in liver enzymes</td>
<td></td>
<td>Additive effect with IFN-α or anti-retrovirals</td>
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<tr>
<td>Decrease the risk of hepatocellular carcinoma in prior known liver disease patients</td>
<td></td>
<td>Cholelithiasis</td>
<td></td>
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<tr>
<td>May inhibit viral replication</td>
<td></td>
<td>Decrease biliary cholesterol secretion and saturation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increase sustained virological response</td>
<td></td>
<td>Inhibit cholesterol crystal nucleation</td>
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<tr>
<td>Additive effect with IFN-α or anti-retrovirals</td>
<td></td>
<td>Dissolution of cholesterol gallstones</td>
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TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; CRP: C-reactive protein; INF-α: interferon alpha
adeovir, tenofovir, or entecavir) showed synergistic antiviral activity [40]. This interaction seemed to be favorable with all four available anti-HBV nucleoside analogues, and as the relative concentration of simvastatin was raised, the overall favorability of the interactions progressively increased.

**CHOLELITHIASIS**

Cholesterol hypersaturation of bile has been described to be important pathophysiological mechanism in the production of gallstones. A considerable number of studies have demonstrated that statins have a potential benefit in the treatment of cholesterol gallstones [41-43]. The mechanisms proposed to explain how statins decrease cholesterol gallstones include: decreased biliary cholesterol secretion and saturation, inhibition of cholesterol crystal nucleation, dissolution of cholesterol gallstones, and an anti-inflammatory effect [41] (Table I). In studies of animal models with prairie dogs, which have similar biliary composition to humans, the administration of lovastatin in dogs fed with a high-cholesterol diet for 21 days was associated with no cholesterol gallstone formation compared with controls (cholesterol-fed animals) (p< 0.005) [42]. It was also shown that statin use in prairie dogs decreased both hepatic and gallbladder bile cholesterol, altered bile acid composition, and induced 79% dissolution of gallstones compared with placebo [43].

These encouraging results are supported by data in short-term trials in humans, as observed in a control study of ten volunteers who were administered 40 mg of lovastatin for a period of five to six weeks [44]. In this study, biliary cholesterol secretion was significantly reduced, from 143 μmol/h to 96 μmol/h, p<0.02. Another study tested the effect of long-term trials in humans, as observed in a control study of ten volunteers who had not filled a prescription for more than 12 months, had an increased risk of developing gallstones compared with active statin users (OR 1.39, 95% CI 1.19-1.61) [47].

The Nurses' Health Study, which evaluated the relationship between the abdominal circumference and waist to hip ratio and risk of cholecystectomy, also analyzed the use of statins in 2,479 cases during a 10-year period and its relationship to the incidence of cholecystectomy [48]. This analysis demonstrated a relative risk reduction of 0.88 (95% CI, 0.78-0.99) in statin users, and the risk was lower for those on statins longer than two years compared to those in treatment for less than two years (RR 0.81, 95% CI 0.68-0.97 versus RR 0.92, 95% CI 0.80-1.07, respectively). Another case-control study including 27,035 cases, showed similar associations between long-term statin use (>1 year) and the risk for cholecystectomy (RR 0.58, 95% CI 0.50 - 0.68) compared with its short-term use [49].

**PANCREATITIS**

Pancreatitis related to statin use has been described in multiple observational studies, but a recent meta-analysis of 16 placebo-statins trials with 113,800 participants, with normal or mildly elevated lipid levels, demonstrated a reduction of pancreatitis among statin users (RR 0.77 95% CI 0.62-0.97, p=0.01) [45]. Simvastatin was tested in ten patients with hyperlipidemia, using doses of 20 and 40 mg, and it was observed that cholesterol saturation index decreased by 24% after seven weeks of treatment, p<0.01 [46].

The long-term use of statins has demonstrated a decreased incidence of cholelithiasis. A population-based case-control study of 32,494 patients observed a decreased risk for gallstone disease in statin users compared with non-users, OR 0.76 (95% CI 0.67-0.86). It also demonstrated that prior statin users who had not filled a prescription for more than 12 months, had an increased risk of developing gallstones compared with active statin users (OR 1.39, 95% CI 1.19-1.61) [47].

**Table II. Ongoing randomized clinical trials with statins on various gastrointestinal pathologies.**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intervention</th>
<th>Patient number</th>
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<tbody>
<tr>
<td>Simvastatin in colorectal surgery</td>
<td>Simvastatin vs placebo</td>
<td>140</td>
</tr>
<tr>
<td>Rosuvastatin in patients with stage I or stage II colon cancer removed by surgery</td>
<td>Rosuvastin vs placebo</td>
<td>1740</td>
</tr>
<tr>
<td>Crossover evaluation of effect of atorvastatin on pharmacokinetic of irinotecan in colorectal cancer patients receiving leucovorin</td>
<td>Atorvastatin plus leucovorin</td>
<td>26</td>
</tr>
<tr>
<td>Trial of capecitabine/ciaplatin plus simvastatin in advanced gastric cancer patients</td>
<td>Simvastatin vs placebo</td>
<td>244</td>
</tr>
<tr>
<td>Study to evaluate the efficacy of pravastatin on advanced gastroesophageal cancer</td>
<td>Pravastatin vs control</td>
<td>146</td>
</tr>
<tr>
<td>Atorvastatin, oligofructose-enriched inulin, or sulindac in preventing cancer in high risk patients</td>
<td>Atorvastatin/oligofructose-enriched inulin/ sulindac/placebo</td>
<td>112</td>
</tr>
<tr>
<td>Protocol for correlating enteropathic severity and small intestinal CYP3A4 activity in patients with celiac disease</td>
<td>Simvastatin</td>
<td></td>
</tr>
<tr>
<td>Pravastatin therapy in patients with active Crohn's disease: a pilot study</td>
<td>Pravastatin</td>
<td>40</td>
</tr>
<tr>
<td>Atorvastatin in moderate active Crohn's disease</td>
<td>Atorvastatin</td>
<td>12</td>
</tr>
<tr>
<td>Phase II study of simvastatin plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer.</td>
<td>Simvastatin</td>
<td>50</td>
</tr>
<tr>
<td>Simvastatin plus cetuximab/irinotecan in K-ras mutant colorectal cancer</td>
<td>Cetuximab + irinotecan + simvastatin</td>
<td>52</td>
</tr>
<tr>
<td>Cetuximab and simvastatin in treating patients with advanced or metastatic colorectal cancer</td>
<td>Cetuximab + simvastatin</td>
<td>51</td>
</tr>
<tr>
<td>Simvastatin and panitumumab in treating patients with advanced or metastatic colorectal cancer</td>
<td>Simvastatin + panitumumab</td>
<td>46</td>
</tr>
<tr>
<td>Trial of capecitabine + irinotecan/leucovorin + simvastatin followed by simvastatin maintenance in metastatic colorectal cancer</td>
<td>Simvastatin</td>
<td>258</td>
</tr>
</tbody>
</table>
This reduction could be related as well to the statins effect on the decrease on gallstone formation as mentioned above.

CONCLUSIONS

A significant amount of evidence supports the use of statin therapy in various gastrointestinal pathologies. However, most of the evidence comes from animal or small observational studies, and is limited due to a lack of randomization, and heterogeneity. Therefore, one cannot make firm conclusions. Large, randomized, placebo-controlled clinical trials are warranted and essential in identifying populations of patients with gastrointestinal disorders that may benefit from statins as a primary or adjuvant treatment option.

Presently, there are several undergoing randomized clinical trials that may clarify the use of statin therapy for the different gastrointestinal pathologies (Table II). These studies, in addition to the existing clinical data, should lay the groundwork for future guidelines and recommendations for statin use in these patient populations.

Conflicts of interest: None to declare.

REFERENCES


