Evaluation of Statin Treatment for Nonalcoholic Fatty Liver Disease

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Abstract

Objective: To review if utilizing statin therapy in patients with nonalcoholic fatty liver disease (NAFLD) is safe and efficacious. **Data Sources:** A MEDLINE literature search was performed using the search terms statins, nonalcoholic fatty liver disease, NAFLD, safety, effectiveness, and efficacy. The literature search was not limited to a predetermined set of dates. The literature search included information from 2003 until February 2016. Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** All English-language randomized controlled trials, case reports, meta-analyses, and guidelines assessing the use of statins in patients with NAFLD were evaluated. **Data Synthesis:** Clinical data demonstrate that statins can increase serum transaminases; however, these effects appear to be dose dependent. Data show that statins do not exacerbate liver injury. The Statin Liver Safety Task Force indicates that statins are safe to use in patients with chronic liver diseases and compensated cirrhosis. Studies conducted to determine if statins are efficacious have been limited to small trials or case reports. However, data suggest that statins can reduce elevated serum transaminases and improve liver histology. **Conclusions:** Guidelines indicate that statins can be used to treat dyslipidemia in patients with NAFLD and nonalcoholic steatohepatitis. Statins may be a viable treatment option for NAFLD in patients who have an increased cardiovascular risk. Additional large, randomized controlled trials need to be conducted in order to confirm the beneficial effects of statins in NAFLD.

Keywords

nonalcoholic fatty liver disease, NAFLD, statin, safety, efficacy

Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in the United States.¹ The prevalence of NAFLD is steadily increasing due to its association with central obesity, diabetes, hypertension, hyperlipidemia, and metabolic syndrome.¹ According to the American College of Gastroenterology, 1 in 3 to 1 in 5 adults have NAFLD.¹ Current treatment options include weight loss management for obese patients, increasing physical activity, and maintaining a balanced diet. Alternative treatment strategies being evaluated include utilization of lipid lowering medications (ie, statins), insulin sensitizers (ie, thiazolidinediones), and antioxidants (ie, vitamin E). Based on the comorbidities commonly associated with NAFLD (eg, hypertension, diabetes mellitus, hyperlipidemia, etc), statin therapy is a logical consideration.

Nonalcoholic fatty liver disease is the accumulation of fat in the liver in individuals who drink little to no alcohol.² NAFLD is divided into 2 types: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH).³ NAFL is hepatic steatosis not associated with inflammation. NAFL can lead to NASH, which is hepatic steatosis associated with hepatic inflammation that may or may not have fibrosis present.³ The primary factors implicated in causing NAFLD include insulin resistance and free oxygen radical species or oxidated injury.⁴

According to the literature, hepatic steatosis is a manifestation of excessive triglyceride accumulation in the liver.⁴ Statins reduce triglycerides, which will decrease excessive accumulation in the liver. In addition, statins have pleiotropic effects, which include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques.⁵ Patients with NAFLD often have atherogenic dyslipidemia such as elevated low-density lipoprotein (LDL) in which statins effectively reduce. There is growing evidence that suggests a strong association between NAFLD and the risk of cardiovascular disease. Patients with NAFLD have a higher cardiovascular disease mortality rate than the general population. Patients with NAFLD typically meet the diagnostic criteria for metabolic syndrome and therefore have multiple risk factors for cardiovascular disease.⁶ A systematic review confirms that NAFLD is strongly associated

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with increased carotid-artery intimal medial thickness and an increased prevalence of carotid atherosclerotic plaques.⁶ Statins have been proven to be effective for primary and secondary prevention of cardiovascular disease.

However, there are 2 predominate barriers hindering the use of statins for NAFLD. There is the concern regarding statin-induced hepatotoxicity and the lack of evidence available demonstrating the effectiveness of using statins to treat NAFLD. The purpose of this review is to evaluate the safe and effective use of statin therapy in the treatment of NAFLD.

Data Sources

A MEDLINE literature search was performed in order to identify articles addressing the safety and efficacy of using statins in patients with NAFLD. The search was conducted using the search terms statins, nonalcoholic fatty liver disease, NAFLD, safety, effectiveness, and efficacy. Search limits included human studies published in English. The literature search was not limited to a predetermined set of dates. After conducting the literature search, information from 2003 until February 2016 was reviewed. Additional references were identified from a review of literature citations.

Safety

Statin-induced hepatotoxicity is associated with asymptomatic elevations of serum aminotransferases within the first 12 weeks of therapy, with no histopathological liver changes.⁷ There have been numerous phase 2 and 3 clinical trials that demonstrate elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Onofrei et al⁸ outlined several studies providing evidence that statin usage is associated with elevated transaminases. One retrospective analysis revealed that out of the 2587 patients with elevated baseline liver function tests (LFTs), 342 of those patients were exposed to statin therapy. AST/ALT elevations have also been shown to be dose dependent.⁹ Typically, standard doses of statins have little to no effect on LFTs.⁹ However, the maximum dosages of lovastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin have been associated with modest but notable increases in transaminase levels.⁹ These elevations created concern that statins could potentially exacerbate liver disease. These concerns further resulted in drug manufacturers recommending that statin therapy should be avoided in patients with underlying liver disease or unexplained aminotransferase elevations. Historically, it was recommended that patients taking statin medications should have their LFTs monitored at baseline, 12 weeks after initiation or dose increase, and periodically thereafter.⁸ However, spontaneous elevations in aminotransferase levels has been associated with transient increases

attributed to cholesterol reduction with statin treatment, diabetes mellitus, obesity, alcohol consumption, or other medications.⁸ In order to confirm whether statin therapy can contribute to or cause significant liver damage, multiple studies have been conducted. The Merck Worldwide Adverse Event Database reviewed 232 cases of acute liver failure associated with lovastatin and found an estimated risk of fulminant liver failure to be 2 per 1 million patients.⁷ In the United States, from 1990 to 2002, 51 741 liver transplantations were performed. Of those transplantations, only 3 of the surgeries were related to statin therapy.⁸

Avins et al¹⁰ conducted a retrospective cohort study to assess the hepatic effects of lovastatin exposure in patients with liver disease. The primary outcome was to determine if there was a pattern of liver-test abnormalities associated with a poor prognosis among patients with drug-induced liver disease based on Hy's law. According to Avins et al, Hy's law is defined as a "liver test profile that is associated with a particularly poor prognosis for patients with drug-induced liver disease."^{10(p327)} Secondary outcomes included liver injury or the development of either clinical cirrhosis or liver failure. Lovastatin exposure was associated with a lower incidence of moderate or severe liver injury as well as the occurrence of either cirrhosis or liver failure. Based on the results, the authors concluded that lovastatin was not associated with an increased risk of adverse hepatic outcomes.

Kiortsis et al¹¹ conducted a study to examine the effects of statins and fibrates on liver enzymes in obese patients. Participants either received fluvastatin (40 mg/day), atorvastatin (10-20 mg/day), micronized fenofibrate (200 mg/day), ciprofibrate (100 mg/day), or gemfibrozil (900 mg/day). At baseline, approximately 9.1% of the patients had a moderate elevation of at least one liver enzyme. After 8 weeks and at the conclusion of the study, no significant change was observed in the mean values of serum liver enzymes. Patients receiving atorvastatin 20 mg did have higher serum transaminases compared to patients receiving atorvastatin 10 mg. However, this difference was not statistically significant. The Kiortsis et al study demonstrates that statins do not contribute to the progression of liver disease, although it does support the notion that elevations in serum transaminases due to statin therapy are dose dependent.¹¹ To date, there has not been any convincing evidence to suggest that dose-dependent increases in serum transaminases are associated with liver damage. Long-term, large randomized trials comparing atorvastatin 80 mg to lower statin doses or placebo have not reported any hepatitis or liver failure.¹²

Lewis et al¹³ examined the efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with stable chronic liver disease. Patients in this multicenter, randomized, double-blind, placebo-controlled, parallel-group trial received either pravastatin 80 mg or placebo. According to the study,

Safety was analyzed by the proportion of subjects who developed at least 1 ALT value greater than or equal to 2 times the upper limit of normal for those with a normal ALT level at baseline or a doubling of the baseline ALT for those with elevated ALT at the baseline during 36 weeks of treatment.

Approximately 64% of the patients had NAFLD and 23% had chronic hepatitis C.¹³ Throughout the study, patients in the pravastatin group had a lower ALT level compared to placebo; however, the difference was not significant.

With the available literature demonstrating that statins are safe to use in patients with liver disease, the Statin Liver Safety Task Force has released recommendations regarding the use of statins. In 2006, the Task Force recommended that routine liver enzyme testing should not be required. Furthermore, they recommend that LFTs drawn at baseline, monitoring LFTs at 12 weeks, and periodically during therapy was no longer necessary. In 2012, the Food and Drug Administration approved modifications to the labeling of statin medications supporting the decision of the Task Force by stating “that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter.”

Since 2012, further studies have been published demonstrating the safety of statin use in patients with NAFLD. Oni et al assessed the association of statin use with NAFLD and the severity of liver fibrosis among NAFLD individuals. In the study, 49% of the 552 individuals using statins had a diagnosis of NAFLD. At the conclusion of the study, there was no significant association between statin use and fatty liver index or severe fibrosis.¹⁴

With regard to NAFLD, the Task Force indicated that statins are safe to use in patients with chronic liver diseases and compensated cirrhosis.¹⁵ This recommendation by the Task Force dispels the previous practice of avoiding statin therapy in patients with liver disease.

Efficacy

Studies evaluating treatment of NAFLD have focused on demonstrating positive histological changes and/or reducing elevated liver enzymes. The Rallidis et al¹⁶ and Ekstedt et al¹⁷ studies both focused on the histological changes due to statin therapy. Rallidis et al¹⁶ evaluated pravastatin on 5 patients with elevated baseline liver enzymes (<3 times ULN) and biopsy-proven NASH. After 6 months of treatment, pravastatin improved liver histology with no elevations in aminotransferases. Ekstedt et al¹⁷ was a retrospective study that assessed liver histology in 68 patients during a 10.3 to 16.3 year follow-up. At the conclusion of the study, the prevalence of NASH in the statin cohort did not change from baseline. However, the prevalence of NASH in the nonstatin cohort increased from 41% at baseline to 65% at the conclusion of the study.

Hatzitolios et al¹⁸ conducted a study to examine the efficacy of omega-3 fatty acids, atorvastatin, and orlistat in patients with NAFLD and dyslipidemia. Patients were divided into 3 groups: patients with hypertriglyceridemia received omega-3 fatty acids, patients with hypercholesterolemia received atorvastatin 20 mg, and overweight patients received orlistat. A reduction in serum transaminase levels and resolution of fatty liver determined by ultrasonography were utilized to assess efficacy. After 24 weeks of treatment, serum transaminase levels decreased significantly in each group; and ultrasonography demonstrated normal liver echopattern in 61% of patients receiving atorvastatin 20 mg.

A 2-year open-label study using atorvastatin 10 mg in patients with NASH and hyperlipidemia showed a statistically significant reduction ($P < .001$) of aminotransferase levels. However, this study was conducted with only 31 patients.¹⁹ Another small pilot study demonstrated significant reduction in serum aminotransferase and lipid levels with atorvastatin 10 to 80 mg daily in patients with dyslipidemia and NAFLD.²⁰ Antonopoulos et al²¹ initiated 23 patients with hyperlipidemia and ultrasonographic evidence of NAFLD on rosuvastatin 10 mg/day. After 8 months of therapy, all 23 patients achieved normalization of aminotransferase and cholesterol levels.

Some of the studies exhibiting significant improvement in LFTs contained a statin being used with additional medications. The St Francis Heart Study²² evaluated the use of atorvastatin and antioxidants for the treatment of NAFLD. The study included participants receiving either a daily combination of atorvastatin 20 mg, vitamin C 1 g, and vitamin E 1000 IU or a matching placebo that did not include active therapy. In addition, all patients received 81 mg of aspirin. Liver to spleen ratios were calculated in order to determine the prevalence of NAFLD. Hepatic steatosis was determined by calculating the difference in the liver attenuation and the spleen attenuation in the patients. A difference in the liver attenuation and spleen attenuation of less than -10 Hounsfield units and a ratio of liver and spleen attenuation of less than one was indicative of hepatic steatosis. At baseline, there were 80 patients with NAFLD. At the conclusion of the study, there was a 71% reduction in the risk of having moderate-to-severe hepatic steatosis in the treatment group.²² A limitation of this study is that the active treatment group received a combination of antioxidants and a statin. This combination makes it difficult to determine the extent to which each agent treats NAFLD.

However, not all of the trials demonstrated positive outcomes. Nelson et al²³ constructed a pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis. Sixteen patients with biopsy-proven NASH were enrolled, and at the conclusion of the study there was no statistically significant improvement in serum aminotransferases, hepatic steatosis, necro-inflammatory activity or stage of fibrosis.

The studies mentioned within this review provide evidence of significant biochemical and histological improvements, but there are limitations with these studies. The majority of these trials has a small sample size, is limited by study design, and has other confounding variables such as concomitant drugs, diet, and exercise.⁸ In 2012, The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease practice guidelines provided recommendations on the usage of statins in patients with NAFLD and NASH.²⁴ The guidelines state that since there is a lack of evidence demonstrating that patients with NAFLD and NASH are at an increased risk for serious drug-induced injury from statins, statins are safe to use when treating dyslipidemia in patients with NAFLD and NASH.

Studies demonstrate that statins are safe to use in patients with NAFLD, but their usage to treat NAFLD or NASH is still controversial. Due to the limitations in study design and small sample sizes, the guidelines do not recommend using statins to treat NASH. According to the guidelines, additional randomized clinical trials with histological endpoints need to be conducted in order to prove the effectiveness of treating NASH with statins.²⁴ The guidelines do not state whether statins can be used to treat NAFLD. Since 2012, there have been a few studies examining the effectiveness of statins for treating NAFLD and NASH. In 2013, a meta-analysis assessed the beneficial and harmful effects of statins on all-cause and liver-related mortality, adverse events, and histological, biochemical, and imaging responses in patients with NAFLD or NASH.²⁵ Based on the findings of the review, the authors concluded that it may be possible that statins improve serum aminotransferase levels as well as ultrasound findings. However, the authors highlighted that the 2 trials reviewed contained a small number of participants and a high risk of bias.²⁵

In 2014, Riche et al²⁶ wrote a case report examining the amelioration of resistant NAFLD with a combination of rosuvastatin and pioglitazone in patients with metabolic syndrome. In the case report, a 47-year-old Caucasian male had an AST and ALT levels of 146 U/L and 88 U/L, respectively, before starting the treatment regimen of rosuvastatin and pioglitazone. On presentation to the clinic, the patient's current medications included Lantus 75 U at night, metformin 1000 mg twice daily, olmesartan/hydrochlorothiazide 40 mg/25 mg daily, aspirin 81 mg daily, over-the-counter fish oil up to 5 g daily, and a daily multivitamin. A trial of vitamin E was initiated for 12 months with no improvement in aminotransferases. After agreeing to start a trial of rosuvastatin 20 mg and pioglitazone 15 mg along with his other medications (including vitamin E), the patient's AST and ALT levels lowered to 38 U/L and 29 U/L, respectively, after 9 months of treatment.

Conclusion and Recommendations

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease guidelines do not recommend statin usage to treat NAFLD, but current literature suggest that statin usage

to treat NAFLD can be a viable option. Providers should consider initiating statin therapy in patients with elevated serum aminotransferases associated with NAFLD due to their safety and potential efficacy. Although randomized clinical trials have shown that statins can potentially increase serum aminotransferases, elevated serum aminotransferase levels do not reflect hepatic injury.⁹ The best indicator of hepatic injury is serum bilirubin levels.⁹ Therefore, statins have been deemed safe to use in patients with chronic liver disease. Furthermore, studies have shown that statins do not exacerbate chronic liver disease. With regard to efficacy, case reports and small clinical trials have demonstrated that statins can normalize elevated serum aminotransferases as well as slow the progression of NAFLD. Individuals with diabetes, hyperlipidemia, and NAFLD may benefit from combining a statin and pioglitazone. As stated, NAFLD increases cardiovascular mortality and diabetes is a coronary heart disease risk equivalent. Utilizing pioglitazone will assist in regulating blood glucose and the pleiotropic effects of statins will provide primary and secondary prevention for coronary heart disease. Since individuals with NAFLD typically present with criteria for metabolic syndrome, physicians should consider calculating the 10-year atherosclerotic cardiovascular disease (ASCVD) risk in NAFLD patients. According to the American Heart Association cholesterol guidelines, individuals between the ages of 40 and 75 without clinical ASCVD or diabetes, a LDL between 70 and 189 mg/dL, and a 10-year ASCVD risk $\geq 7.5\%$ should be initiated on a moderate- to high-intensity statin.²⁷ If a patient with NAFLD has an ASCVD risk greater than or equal to 7.5%, the patient should be initiated on statin therapy. Although this would result in an increase in LFTs due to the usage of moderate- to high-intensity statins, these elevations should be transient. However, in order to validate these findings and potential treatment strategies additional randomized controlled trials need to be conducted in order for statin therapy for NAFLD to become normal practice.

Declaration of Conflicting Interests

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