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Nonalcoholic fatty liver disease and statins

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ABSTRACT

Objective. Nonalcoholic fatty liver disease (NAFLD) is the most frequent cause of elevated transaminase levels and affects approximately one third of the general population. Patients with NAFLD are at increased risk for cardiovascular events, which represent the leading cause of death in this population. We discuss the safety and efficacy of statins in this population.

Materials/methods. We reviewed the most recent literature on the safety of statins in patients with NAFLD and on their effects on liver histology and cardiovascular events.

Results. It appears that statins can be safely administered to patients with NAFLD, including those with elevated transaminase levels (<3 times the upper limit of normal). Post-hoc analyses of randomized controlled trials also suggest that statins might reduce cardiovascular morbidity in this population. On the other hand, there are few and controversial data on the effects of statins on liver histology in patients with NAFLD.

Conclusions. Statins appear to be safe and might also reduce cardiovascular events in patients with NAFLD. Ongoing and future studies will clarify whether statins might also have a role in the treatment of NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as evidence of hepatic steatosis, either by imaging or by histology, in the absence of secondary causes of hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medications (e.g. methotrexate, corticosteroids, amiodarone) or hereditary disorders (e.g. abetalipoproteinemia) [1]. NAFLD includes nonalcoholic fatty liver (NAFL), characterized by isolated hepatic steatosis without other abnormalities in hepatic histology, and nonalcoholic steatohepatitis (NASH), characterized by the presence of steatosis, inflammation, and ballooning with or without fibrosis [1]. NAFLD represents the commonest chronic liver disease and the leading cause of elevated

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal; WOSCOPS, West of Scotland Coronary Prevention Study; CARE, Cholesterol and Recurrent Events; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; CHD, coronary heart disease; GREACE, Greek Atorvastatin and Coronary Heart Disease Evaluation; ATTEMPT, Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; CT, computed tomography.

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transaminase levels in high-income countries [2,3]. Approximately 34% and 12% of the general population has NAFL and NASH, respectively [4,5].

The pathogenesis of NAFLD involves a first step, where free fatty acids accumulate in the liver, particularly in patients with insulin resistance, abdominal obesity, type 2 diabetes mellitus (T2DM) and/or metabolic syndrome (MetS) [6,7]. In the second step, insulin resistance along with inflammation, oxidative stress, hepatocellular apoptosis and iron deposition result in the progression from NAFL to NASH [6,7]. Accordingly, NAFLD is particularly prevalent in patients with abdominal obesity, T2DM and/or MetS [8–10]. Partly due to the association between NAFLD and these cardiovascular risk factors, NAFLD is associated with increased risk for cardiovascular disease (CVD), which represents the leading cause of death in this population [11–13]. Moreover, cross-sectional studies showed that transaminase levels correlate with insulin resistance and low-density lipoprotein cholesterol (LDL-C) levels [14–16]. Several observational studies also reported that elevated transaminases are associated with increased incidence of T2DM and with higher risk for cardiovascular events [16–20].

There are currently limited options for the management of patients with NAFLD. Diet and exercise represent the fist-line treatment, but it is unclear whether they improve fibrosis and long-term adherence is infrequently achieved [1,21]. Regarding pharmacotherapy, pioglitazone and vitamin E appear to improve liver histology [22], but their effects on cardiovascular events in this population are unknown. Moreover, safety concerns limit the use of both agents. Indeed, pioglitazone increases the risk for weight gain, heart failure, fractures and bladder cancer [23–25], whereas vitamin E appears to be associated with higher risk for prostate cancer and all-cause mortality [26,27].

Given the increased cardiovascular risk of patients with NAFLD, multifactorial intervention targeting all cardiovascular risk factors is essential to prevent CVD in this population [1]. Elevated levels of LDL-C levels are a major modifiable cardiovascular risk factor and statins are the agent of choice for lowering LDL-C levels [28–31]. However, treatment with statins might increase transaminase levels and therefore physicians are frequently reluctant to use these agents in patients with NAFLD [30–33]. Nevertheless, accumulating data suggest that statins are safe in this population, reduce transaminase levels and might also decrease cardiovascular morbidity [34,35]. The aim of the present review is to summarize the existing evidence regarding the safety of statins in patients with NAFLD and to discuss the effects of these agents on cardiovascular disease and liver histology in this population.

2. Safety of Statins in Patients with NAFLD

Several observational studies suggested that statins are safe in patients with elevated transaminase levels. In these studies, patients had no evidence of hepatitis B or C or alcohol abuse and therefore the most likely cause of elevated transaminase levels was NAFLD [2,3]. In an early report, patients with elevated transaminase levels were given atorvastatin or simvastatin at a median dose of 10 and 20 mg/day, respectively (n = 342), or were not treated with a statin (n = 2,245) [36]. The incidence of further elevation in transaminase levels was similar in the two groups [36]. Among patients treated with a statin, the incidence of mild-moderate elevation in transaminase levels (<10 times the upper limit of normal (ULN) or <10 times the baseline transaminase levels) was higher in patients with elevated transaminase levels at baseline than in those with normal transaminase levels (n = 1,437) [36]. However, the incidence of severe elevation in transaminase levels (>10 times the ULN or >10 times the baseline transaminase levels) did not differ between the two groups [36]. Another observational study (n = 3,399) in patients with elevated transaminase levels who were treated with lovastatin reported similar findings [37].

Randomized controlled studies also showed that statins are safe in patients with elevated transaminase levels presumably due to NAFLD. In a pooled analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), Cholesterol and Recurrent Events (CARE) trial and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (n = 19,592 patients with coronary heart disease (CHD) or without established CVD), the incidence of further elevation in transaminase levels was similar in patients with elevated transaminase levels (<3 times the ULN) who were treated with pravastatin 40 mg/day (n = 317) and in those who were given placebo (n = 262) [38]. In a post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study (n = 1,600 patients with CHD), 437 patients had elevated transaminase levels (<3 times the ULN) at baseline [34]. Treatment with atorvastatin (mean dose 24 mg/day) resulted in normalization of transaminase levels whereas patients who were not given a statin showed further rises in transaminase levels [34]. In a post-hoc analysis of the Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT) study (n = 1,123 patients with MetS), 326 patients had elevated transaminase levels (<3 times the ULN) at baseline [10]. Treatment with atorvastatin aiming at LDL-C levels <130 or <100 mg/dl (mean dose 24 and 34 mg/day, respectively) resulted in normalization in of transaminase levels in 89% and 94% of the patients, respectively [10]. More recently, a post-hoc analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study (n = 8,888 patients with CHD) reported similar findings in patients treated with higher doses of statins [35]. At baseline, 1,081 patients had elevated transaminase levels (<2 times the ULN) and treatment with either simvastatin 20–40 mg/day or atorvastatin 80 mg/day reduced transaminase levels [35].

Several small studies also showed that statins are safe in patients with NAFLD. In a subgroup analysis of the Dallas Heart Study, patients with hepatic steatosis (diagnosed with magnetic resonance spectroscopy) who were taking statins (n = 54) had similar alanine transaminase (ALT) levels with patients with steatosis who were not on statins (n = 584) [39]. A number of small uncontrolled studies showed that treatment with statins reduces transaminase levels in patients with NAFLD (Table 1) [40–49]. Three larger randomized controlled studies also reported similar findings [50–52]. In the first, 186 patients with NAFLD and MetS but without T2DM