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Statins for patients with nonalcoholic fatty liver?

Although physicians often avoid prescribing statins for patients with nonalcoholic fatty liver, their use has been found to reduce cardiovascular morbidity and mortality—and to lower liver enzymes.

PRACTICE CHANGER

Treat patients with hyperlipidemia and presumed nonalcoholic fatty liver disease with atorvastatin to reduce the risk of cardiovascular events.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single prospective randomized controlled trial (RCT).

Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post hoc analysis. *Lancet*. 2010; 376:1916-1922.

ILLUSTRATIVE CASE

An obese 58-year-old man with type 2 diabetes comes to your office for follow-up. His low-density lipoprotein cholesterol (LDL-C) is 130 mg/dL; triglycerides, 300 mg/dL; alanine transaminase (ALT), 110 units/L; and aspartate transaminase (AST), 120 units/L. The patient's work-up for chronic hepatitis B and C, autoimmune hepatitis, hemochromatosis, and Wilson's disease are negative, and you rule out alcohol misuse based on his medical history. An ultrasound of the patient's liver reveals hepatic steatosis, and you diagnose nonalcoholic fatty liver disease (NAFLD). Should you start him on a statin?

Patients with central obesity, diabetes, hypertension, hyperlipidemia, and metabolic syndrome are at high risk of developing NAFLD. These conditions have increased in prevalence, and NAFLD is now the most common cause of liver disease in the United States.[2] In Western industrialized countries, approximately 30% of the general population and 70% to 90% of patients with diabetes will develop NAFLD.[3] Although most patients are asymptomatic, their liver enzymes are elevated. To diagnose NAFLD, it is necessary to rule out alcoholic hepatitis with a medical history, and viral hepatitis, hereditary hemochromatosis, Wilson's disease, and autoimmune hepatitis with laboratory testing. Ultrasound reveals fat accumulation in the liver.

Treatment for NAFLD has little evidence of benefit

Patients with NAFLD have a much higher mortality rate than that of the general public, primarily because of cardiovascular disease.[4-6] Increased physical activity and weight loss is the only therapy that has solid evidence of a benefit,[7] although other treatments, such as insulin-sensitizing drugs (metformin or pioglitazone), may be beneficial.[8] Surprisingly, atorvastatin has been found to reduce aminotransferase levels in patients with NAFLD,[9,10] but clinicians are often concerned about prescribing a statin for patients with elevated liver enzymes. In one study, 50% of primary care physicians said they would not prescribe statins for patients whose liver enzymes are 1.5× the upper limit of normal (ULN).[11]

STUDY SUMMARY

Statins lower risk of cardiovascular morbidity and mortality

The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study was a randomized, prospective open-label, intention-to-treat trial involving 1600 patients. All had established coronary heart disease (CHD), were younger than 75 years, and had triglycerides <400 mg/dL and LDL-C >100 mg/dL. The study reviewed here—evaluating the risk-to-benefit ratio of using a statin to treat hyperlipidemia in patients with NAFLD—was a post hoc analysis of the GREACE study.[1]

Participants were randomized to either usual care or structured care with atorvastatin, starting at 10 mg/d and adjusted to 80 mg/d to bring the LDL-C level below 100 mg/dL. In the usual care group, treatment included lifestyle changes plus necessary drug treatments (only 30% of those in the usual care group received hyperlipidemia drugs). Patients were followed after medication dose titration, then every 6 months for 3 years. Serum ALT and AST were measured at baseline, at 6 weeks, and every 6 months.

At baseline, mild-to-moderate increases (<3× ULN) in ALT/AST were noted in 437 of the 1600 patients. For these patients, alcoholic hepatitis, chronic hepatitis B and C, Wilson's disease, and autoimmune hepatitis were excluded by history, laboratory tests, and ultrasound, and the elevated liver enzymes were attributed to NAFLD.

The primary endpoints were the first occurrence of any cardiovascular event, including nonfatal myocardial infarction, revascularization, unstable angina, heart failure, and stroke; all-cause mortality; and CHD mortality. The relative risk (RR) for such events was calculated for the 437 patients with elevated liver enzymes, compared with that of patients without abnormal liver tests. Elevated liver enzymes and liver-related adverse events were secondary endpoints.

A cardiovascular event occurred in 10% (22/227) of the patients with elevated liver enzymes who received a statin, and 30% (63/210) of patients who had elevated liver enzymes but did not receive a statin.

There were 3.2 events per 100 patient-years in the atorvastatin group, compared with 10 events per 100 patient-years in those not on atorvastatin, a 68% reduction in RR ($P<.0001$) and an NNT of 15 per year to prevent one cardiovascular event. The risk reduction in cardiovascular events was greater in patients with NAFLD (68%) than in patients with normal liver tests (39%).

An added benefit was the reduction in ALT/AST levels during treatment for patients with NAFLD who were taking a statin, an average decrease of 47% in AST levels and 35% in ALT levels. In addition, 89% of the patients in the statin group had normal ALT, AST, and gamma-glutamyl transferase levels by the end of the 3-year follow-up. Patients with NAFLD who did not receive statins had a 12% increase in AST and ALT by the end of the 3-year study.

Only 10 of 880 patients taking statins developed liver enzymes more than 3× ULN. In 3 of these patients, dose adjustments brought the liver enzymes back to normal. Only 7 (<1%) patients who received a statin had to discontinue therapy because of liver-related adverse effects.

WHAT'S NEW

Liver enzymes improve, with few adverse effects

Preliminary studies have shown an improvement in liver enzymes in patients with NAFLD treated with a statin.[9,10] This is the first study to show survival benefits and significant reduction in major cardiovascular morbidity for such patients, as well.

This is also the first large-scale study that shows that treating NAFLD patients with a statin decreases liver enzyme levels, with minimal adverse effects.

CAVEATS

Differences in groups, few women could skew results

This study cannot be considered the final word on this topic. Patients in the "structured care" group were followed at a university clinic, while those in the "usual care" group were followed by either a family physician or a cardiologist outside the hospital, based on

This is the first study to show survival benefits and significant reduction in major cardiovascular morbidity for patients with NAFLD treated with a statin.

their choice. There may have been other differences in the care received by the 2 groups that could account for the difference in mortality and morbidity reduction.

In addition, study participants had coronary artery disease, and atorvastatin was not used for primary prevention. Moreover, nearly 80% of the study participants were male, which raises the question of generalizability. And this study was a post hoc analysis of the larger GREACE study, which also raises concerns about the validity of findings.

In the absence of a larger prospective RCT, however, this is the best available evidence to support the use of statins in this population, and suggests that treating patients with NAFLD with statins is safe and effective.

CHALLENGES TO IMPLEMENTATION

Extensive Dx tests are costly

Study participants were evaluated to rule out other causes of their abnormal liver tests, with extensive laboratory tests and an ultrasound evaluation of the liver. Such extensive testing may be cost prohibitive in some situations. **JFP**

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References

1. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post hoc analysis. *Lancet*. 2010; 376: 1916-1922.
2. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. *Cleve Clin J Med*. 2008;75:721-728.
3. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002;346:1221-1231.
4. Adams LA, LympJ F, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113-121.
5. Soderberg C, Stal P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology*. 2010;51:595-602.
6. Targher G, Day CP, Bonora E. Risk of cardiovascular diseases in patients with nonalcoholic fatty liver. *N Engl J Med*. 2010; 363:1341-1350.
7. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology*. 2010;51:121-129.
8. Angelico F, Burattin M, Alessandri C, et al. Drugs improving insulin resistance for nonalcoholic fatty liver disease and/or non-alcoholic steatohepatitis. *Cochrane Database Syst Rev*. 2007;(1):CD005166.
9. Hyogo H, Tazuma S, Arihiro K, et al. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. *Metabolism*. 2008;57:1711-1718.
10. Georgescu EF, Georgescu M. Therapeutic options in nonalcoholic steatohepatitis (NASH). Are all agents alike? Results of a preliminary study. *J Gastrointestin Liver Dis*. 2007;16:39-46.
11. Rzouq FS, Volk ML, Hatoum HH, et al. Hepatotoxicity fears contribute to underutilization of statin medications by primary care physicians. *Am J Med Sci*. 2010;340:89-93.