CLINICAL INQUIRIES

From the
Family Physicians
Inquiries Network

Can patients with steatohepatitis take statins?

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EVIDENCE-BASED ANSWER

Patients with steatohepatitis who take HMG Co-A reductase inhibitors (statins) lower their elevated liver enzymes and show evidence of improvement in fatty liver on follow-up imaging (strength of recommendation [SOR]: **C**, based on very small, short-term prospective studies).

Statins do not further increase

transaminase levels for patients with pre-existing transaminase elevations (SOR: **B**, based on 2 retrospective cohort studies). However, for patients with decompensated liver disease or advanced cirrhosis, balance the benefits of statins against the risks (SOR: **C**, based on expert opinion).

CLINICAL COMMENTARY

Remain cautious in prescribing statins for those with nonalcoholic steatohepatitis
It is encouraging to see that statins may not worsen nonalcoholic steatohepatitis (NASH) and can potentially improve the process.
However, these conclusions are supported by small clinical trials, and clinicians should remain cautious in prescribing statins for patients with NASH.

Importantly, if liver enzyme elevations are revealed during baseline examinations, consider statins only if a systematic work-up is unrevealing and suggests only NASH.⁷⁻⁹ However, I generally avoid statins for those

with more than mild to moderate elevations (greater than 100). Before starting statins, I inform patients of the small but potential risk of worsening hepatotoxicity and the importance of close follow-up. If the patient is agreeable, obtaining hepatic enzymes after each statin dose change and periodically after cholesterol goals are achieved is integral in the successful management of the NASH patient requiring statin therapy.

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■ Evidence summary

A prospective study¹ evaluated 5 patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) who took 20 mg of pravastatin daily for 6 months. Liver enzyme levels at baseline were no more than 3 times the upper limit of normal. All 5 patients had normalized liver enzymes at the end of the study.

A 6-month unblinded study² found similar results among 44 adult patients with biopsy-confirmed NASH. Twenty-seven hyperlipidemic patients (aged 50 ± 1.4 years) with an average alanine aminotransferase (ALT) of 81.8 U/L took 10 mg of atorvastatin daily. Seventeen normolipidemic patients (aged 43.7 \pm 1.8 years) with an average ALT of 76.0 U/L took ursodeoxy-

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FAST TRACK

Inform patients of the small risk of worsening liver toxicity and the importance of close follow-up cholic acid (UDCA) 13–15 mg/kg/d for the same duration; 59% of atorvastatin-treated patients normalized liver enzyme levels compared with 23% in the UDCA group. On computed tomography scanning, both groups showed improvement in liver densities, suggesting improvement of fatty liver.²

Another study³ included patients with biopsy-confirmed fatty liver and elevated ALT levels greater than 1.5 times the upper limit of normal. In this 24-week study, 23 predominantly hypertriglyceridemic patients took omega-3 fatty acids, 5 mL 3 times daily, 28 hypercholesterolemic patients took atorvastatin 20 mg daily, and 21 dyslipidemic patients with a body mass index >27.0 took orlistat 120 mg 3 times daily. ALT levels decreased in all 3 groups during the study. Ultrasonography showed normal liver echo pattern at the end of treatment for 35% of omega-3 patients, 61% of atorvastatin patients, and 86% of orlistat patients. No serious adverse events were observed.

Two retrospective studies of patients with baseline elevated transaminases who took statins showed no significant increase in transaminase levels during treatment compared with patients with elevated transaminases who did not take statins. One study4 reviewed electronic medical records for patients with preexisting elevated liver enzymes who initiated statin therapy (atorvastatin, simvastatin, or fluvastatin) and had follow-up labs drawn 6 months later (cohort 1, n=342). The comparison groups included patients with normal liver enzymes who initiated statins (cohort 2, n=1437) and patients with elevated baseline liver enzymes who did not take statins (cohort 3, n=2245). At followup, 4.7% of cohort 1 patients had mild-tomoderate elevations in liver enzymes, which did not differ significantly (P=.2)from those in cohort 3. Within cohort 2, 1.9% experienced mild-to-moderate elevations of transaminases (defined as less than 10 times the upper limit of normal).

Another retrospective cohort study⁵ of patients with preexisting elevated liver enzymes found comparable results with

lovastatin. Among lovastatin patients (n=135), 6.6% had mild-to-moderate elevations in transaminases during therapy vs 11% of the cohort of patients with pre-existing elevated liver enzymes who did not take statins. This difference was not statistically significant (P=.2).

Recommendations from others

The National Cholesterol Education Project⁶ states that "the incidence of clinically important transaminase elevations in the large statin trials is the same for statins as for placebo. Progression to liver failure is exceedingly rare, if it occurs." They further state that the use of statins for persons with decompensated liver disease or advanced cirrhosis depends on clinical judgment, but that their use in NASH is considered safe.

The FDA states that statins are contraindicated in cholestasis and active liver disease, and that statins should be discontinued when liver enzymes increase to 3 times the upper limits of normal.

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