commentary

Does inhibition of apolipoprotein B synthesis produce foie gras?[1]

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The development of statin drugs has revolutionized the treatment of hyperlipidemia and cardiovascular disease. With the use of statins we are now able to markedly lower LDL cholesterol levels. For example, with high doses of potent statins we can reduce LDL cholesterol levels by more than 50% (1). However, despite these impressive reductions there is still the need for additional therapeutic agents in a significant number of patients. First, patients with genetic disorders of lipoprotein metabolism, such as patients with familial hypercholesterolemia who have marked elevations of LDL cholesterol, seldom achieve LDL cholesterol levels less than 100 mg/dl even with aggressive statin treatment alone (2). Second, with the trend toward more stringent LDL lowering goals (i.e., LDL cholesterol <70 mg/dl) many patients are unable to achieve these low values with statin therapy alone. For example, in the Treat to New Target study, atorvastatin 80 mg resulted in a mean LDL of 77 mg/dl, demonstrating that a significant percentage of patients with coronary artery disease will not reach an LDL goal of less than 70 mg/dl with potent statin therapy alone (3). Finally, a significant percentage of patients cannot tolerate statin therapy or can only take low doses of statins because of muscle symptoms (4). Thus, there is a clear need for additional therapies to lower LDL cholesterol levels.

Mipomersen is a second generation antisense oligonucleotide that targets apolipoprotein B-100 (5, 6). Antisense oligonucleotides are short single-stranded synthetic analogs of nucleic acids that bind specific mRNAs and thereby prevent the synthesis of specific proteins. Mipomersen inhibits apolipoprotein B-100 synthesis in the liver, thereby inhibiting the formation and secretion of apolipoprotein B lipoproteins by the liver (5, 6). As expected, studies have shown that mipomersen treatment results in a reduction in serum cholesterol levels (5, 6). In this issue of the *Journal of Lipid Research*, Visser et al. (7) show that adding mipomersen (200 mg given subcutaneously weekly) to statin therapy results in a further reduction in LDLc (–22%), non-HDLc (–21%), Lp(a) (–19.6%), and apolipoprotein B (–20%). There was a suggestion of a reduction in VLDLc and serum triglyceride levels but these changes did not achieve statistical significance, perhaps because of the small number of patients studied. HDLc and apolipoprotein A levels were not altered by mipomersen therapy. These results are similar to what has been observed in other studies using mipomersen (5, 6, 8).

Mipomersen thus appears to be a potentially useful agent to lower apolipoprotein B-100 containing lipoproteins and could be used in combination with statin therapy or alone in statin intolerant patients. However, a major concern with therapeutic agents that inhibit hepatic VLDL production is the development of fatty liver. Patients with familial hypobetalipoproteinemia, a genetic disorder frequently due to mutations in the apolipoprotein B gene resulting in truncated forms of apolipoprotein B-100, characteristically exhibit very low LDL cholesterol levels and appear to be protected from cardiovascular disease (9). However, many patients with familial hypobetalipoproteinemia have fatty livers, presumably due to the inability of the liver to secrete triglyceride in VLDL particles (10, 11). Similarly, treatment with microsomal triglyceride transfer protein inhibitors, which block the transfer of triglyceride to apolipoprotein B-100 and thereby decrease VLDL formation and secretion, also results in a marked increase in hepatic triglyceride storage (12). Together, these observations raise the possibility that the mipomersen induced inhibition of apolipoprotein B-100 synthesis might also result in the accumulation of triglyceride in the liver.

The study by Visser et al. (7) determined the effect of 15 weeks of mipomersen treatment (200 mg subcutaneously each week) on triglyceride accumulation in the liver. Patients included in this study had familial hypercholesterolemia and were already on statin therapy. The average age of the patients was in the forties with an average BMI of 27. Baseline LDLc levels were 155 mg/dl, HDLc 47 mg/dl, and triglycerides 102 mg/dl. Hepatic triglyceride levels were measured by magnetic resonance spectroscopy at

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baseline and after 4 and 15 weeks of treatment. The authors report that there was a trend toward an increase in triglyceride accumulation in the liver of patients treated with mipomersen compared with placebo treated controls (75% increase that was not statistically significant) but 90% of patients remained within the normal range. Of note is that the triglyceride accumulation appeared to increase with the duration of treatment being greater at 15 weeks than at 4 weeks. One subject (10% of subjects) exceeded the upper limit of normal for triglyceride in the liver but with extended follow-up off of mipomersen therapy (35 weeks) the hepatic triglyceride content returned to normal levels. In this study, there were no significant changes or abnormalities in transaminase levels or other tests of liver function. However, in other studies, increases in serum tranaminases greater than three times the upper limit of normal have been observed in a significant number of patients treated with mipomersen (ref. 28 of Visser et al.).

Why inhibition of apolipoprotein B-100 synthesis does not appear to result in marked accumulation of triglyceride in the liver while inhibition of microsomal triglyceride transfer protein leads to marked triglyceride accumulation is unclear. Similar differences in effect of microsomal triglyceride transfer protein inhibition and apolipoprotein B-100 inhibition have also been observed in animal studies (13, 14). Of note, inhibition of apolipoprotein B-100 synthesis in rodents downregulated the expression of a number of key genes involved in fatty acid and triglyceride metabolism including stearoyl-CoA desaturase 1, fatty acid binding protein 2, sterol regulatory element binding protein-1c, and fatty acid synthase (14). This additional effect of inhibiting apolipoprotein B-100 synthesis could perhaps explain the differences in hepatic triglyceride accumulation.

Although the study of Visser et al. suggests that mipomersen treatment does not result in a significant accumulation of triglyceride in the liver, one needs to consider a number of caveats. First, the number of patients studied was very small. Second, the duration of the study was only 15 weeks and it is possible that longer studies will reveal greater triglyceride accumulation in the liver. The maximal effect of mipomersen on serum lipids can take an extended period of treatment and the development of fatty liver may follow a similar time course. Third, the patients in this study were at low risk for the development of fatty liver. If one had included patients with diabetes, obesity, metabolic syndrome, hypertriglyceridemia, or heavy ethanol intake, who are at high risk for the development of fatty liver, the effect of inhibiting apolipoprotein B-100 synthesis may have been more dramatic. Fourth, would different dietary conditions, such as a high fat or high carbohydrate diet, potentiate the effects of apolipoprotein B-100 inhibition on triglyceride accumulation in the liver? Finally, would the effect of other disorders that lead to fatty liver be potentiated in patients treated with mipomersen? For example, sepsis frequently induces fatty liver and could simultaneous inhibition of apolipoprotein B-100 synthesis worsen this effect (15).

In conclusion, the answer to the question does the inhibition of apolipoprotein B synthesis produces foie gras is not under the conditions studied. However, whether under other circumstances fatty liver will become a clinical problem with inhibition of apolipoprotein B synthesis remains to be determined. Like many issues in science and medicine, additional studies are required to definitively answer this key question.

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