



DYSLIPIDEMIA

Phase III trial of mipomersen in heterozygous FH

Various studies have shown that LDL-cholesterol and apolipoprotein B levels are reduced with mipomersen use in individuals with homozygous familial hypercholesterolemia (FH). However, many clinicians, including several on an FDA panel assessing the drug for use in patients with homozygous FH, have expressed concerns about the adverse effects that mipomersen has on the liver. These effects include elevations in hepatic transaminase levels and in hepatic fat. Nevertheless, on 18 October 2012, an FDA panel voted 9–6 in favor of recommending that the FDA approve mipomersen for use as an add-on therapy in patients with homozygous FH who are already on other lipid-lowering therapy and on a low-fat diet.

For the setting of heterozygous FH and CAD, a new phase III trial has compared mipomersen (200 mg weekly by self-administered subcutaneous injection) with placebo in 124 patients who were already taking maximally tolerated doses of statin. The primary efficacy end point was change

in LDL-cholesterol level from baseline at 28 weeks (or 2 weeks after last dose of mipomersen or placebo in those who did not complete the study). Safety was assessed via various outcome measures.

Levels of LDL cholesterol were reduced in patients assigned mipomersen, but not in those assigned placebo (–28.0% vs +5.2%, $P < 0.001$). Almost half of patients (45.1%) assigned mipomersen, but only 4.9% of those assigned placebo, achieved the target LDL-cholesterol level of < 2.6 mmol/l (100 mg/dl). The mipomersen-associated reduction in LDL-cholesterol level was greater in females (–40.6%) than in males (–20.0%).

Notably, however, 10.8% of patients receiving mipomersen, but none of the patients in the placebo group, withdrew from treatment during the trial. Injection-site reactions occurred about twice as often in patients receiving mipomersen and change in hepatic fat content was significantly greater in the mipomersen group (4.9% vs 0.4%, $P < 0.001$). Moreover,

alanine-aminotransferase elevations greater than three times the upper limit of normal occurred in 14.5% of individuals on mipomersen versus 2.4% on placebo. These elevations were confirmed ≥ 1 week later in 6% and in none of the patients assigned to mipomersen and placebo, respectively.

The authors of the report highlight that the “clinical implications of such increases in hepatic fat, and transaminase elevations, and the overall safety ... must be elucidated in longer-term studies”. They also point out that future studies are needed to determine whether titration to lower doses of mipomersen would be safer, but associated with preserved efficacy.

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Original article Stein, E. A. *et al.* Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation* doi:10.1161/CIRCULATIONAHA.112.104125