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Efficacy and safety of mipomersen in treatment of dyslipidemia: A meta-analysis of randomized controlled trials

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BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is the primary target of lipid-lowering therapy in people at risk for cardiovascular diseases. Mipomersen inhibits apolipoprotein B-100 (apoB) synthesis and causes reduction in LDL-C by reducing apoB.

OBJECTIVE: We aimed to perform a meta-analysis of all published randomized controlled trials comparing safety and efficacy of mipomersen with placebo in adults with dyslipidemia.

METHODS: We searched PUBMED, CENTRAL, and EMBASE from inception through March 2014 and used random-effects model to compute the effect size.

RESULTS: We identified 8 randomized controlled trials (n = 462). Mipomersen compared with placebo significantly reduced LDL-C by 32.37% (95% confidence interval, 25.55–39.18; $P < .00001$), total cholesterol by 24.18% (18.54–29.83; $P < .00001$), very low–density lipoprotein cholesterol by 21.59% (9.16–34.02; $P = .0007$), non–high-density lipoprotein cholesterol (HDL-C) by 30.83% (23.92–37.74; $P < .00001$), and triglycerides by 36.26% (22–50.54; $P < .00001$). It also significantly reduced apoB, lipoprotein(a), and apolipoprotein A1. However, mipomersen did not significantly change HDL-C levels. In safety analysis, mipomersen compared with placebo increased the risks of injection-site reaction (risk ratio, 2.05; 95% confidence interval, 1.39–3.04; $P = .0003$), flu-like symptoms (1.63; 1.22–2.17; $P = .0008$), alanine aminotransferase ≥3X upper limit of normal (4.44; 1.67–11.86; $P = .003$), and hepatic steatosis (3.85, 1.39–10.67; $P = .01$). The risks of alanine aminotransferase ≥10X upper limit of normal did not reach statistical significance (1.57; 0.32–7.6, $P = .58$).

CONCLUSION: Mipomersen resulted in a significant improvement in lipid parameters except for HDL-C and increased the risks of injection-site reactions, flu-like symptoms, and hepatic steatosis compared with placebo.

Author contributions: R.P. and K.D. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R.P. and K.D. contributed to the study concept and design; acquisition, analysis, or interpretation of data; drafting of the article; critical revision of the article for important intellectual content; statistical analysis; and study supervision. S.K. contributed to acquisition, analysis, or interpretation of data; critical revision of the article for important intellectual content; and study supervision.

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Introduction

The serum level of low-density lipoprotein cholesterol (LDL-C) is directly linked to the rate of new onset of coronary heart disease (CHD) and progression of an established CHD.[1–4] On the other hand, high-density lipoprotein cholesterol (HDL-C) levels are inversely correlated with risk of CHD.[5] LDL-C is the primary target of lipid-lowering therapy in people at risk for cardiovascular disease, which is the leading cause of death in the industrialized countries.[6] According to Centers for Disease Control and Prevention, 71 million American adults (33.5%) have high LDL-C less than half of which get treatment to reduce its levels and 1 of every 3 who get treatment have this condition under control.[7] Despite the advent of potent statins and use of combination lipid-lowering therapy, a substantial proportion of patients at high risk of CHD remain unable to achieve optimal LDL-C.[8]

Mipomersen, an antisense oligonucleotide designed to enhance destruction of the messenger RNA for apolipoprotein B-100 (apoB) provides a means of reducing the synthesis of this major apolipoprotein and therefore the number of very low–density lipoprotein (VLDL) and possibly LDL molecules leaving the liver. This produces a reduction of these apoB-containing lipoproteins in the plasma.[9] Statins and other LDL-lowering drugs such as ezetimibe and bile acid sequestrants act through increasing LDL receptors and thereby enhancing clearance. By providing a totally new mechanism of action, mipomersen may be useful in patients with defective or absent LDL receptors or who do not respond fully to existing drugs. In randomized controlled trials, a significant reduction in LDL-C has been observed in patients with familial hypercholesterolemia[10–12] and in patients with dyslipidemia on statin therapy[13,14] or statin intolerance.[15] To better define its efficacy and safety, we performed a meta-analysis of current randomized trials of mipomersen in adults (≥18 years) with dyslipidemia.

Methods

Data sources and search strategy

We wrote a study protocol in accordance with the PRISMA statement.[16] We searched MEDLINE, EMBASE, and Cochrane CENTRAL Register of Controlled Trials for publications since inception through March 2014 without language restriction. The search terms were "mipomersen" OR "apolipoprotein B synthesis inhibitor" with restriction to randomized design ("randomized controlled trials" OR "controlled clinical trials" OR "comparative study"). Two authors (R.P. and K.D.) independently performed the database search, and disagreement was resolved by consensus. A hand search was performed for all relevant references from the selected articles.

Study selection

The flow diagram for study selection is shown in Figure 1. We included randomized controlled trials comparing mipomersen vs placebo in adult patients (≥18 years) with dyslipidemia in the meta-analysis. We excluded studies with nonrandomized designs, healthy volunteers, pediatric patients, animals, and abstracts without full-text publications.

Data extraction

Two authors (R.P. and K.D.) extracted data from the selected studies in duplicate using standardized data-extraction form. We obtained data on study and patient characteristics, indication(s) of mipomersen use, dosages of mipomersen, duration of follow-up, and major safety and efficacy outcomes as described in the following. In intervention arm, data were only extracted for mipomersen dose of 200 mg if the studies used variable doses,[10,13,17] whereas all patients in the control arm were included in the analysis. Disagreement was resolved by consensus.

Major outcomes

Efficacy outcomes were percentage change in LDL-C, HDL-C, triglycerides, non–HDL-C, VLDL cholesterol (VLDL-C), total cholesterol, and lipoprotein(a), apolipoprotein A1, and apolipoprotein B. The safety outcomes were risks of elevated alanine aminotransferase (ALT) >3X upper limit of normal (ULN) and >10X ULN, hepatic steatosis, flu-like symptoms, and injection-site reaction.

Statistical analysis

We pooled the continuous variables as the difference in percentage change in mean and the categorical variables as risk ratio (RR), both with 95% confidence interval (CI). We used crude events from each study to compute RR with 95% CI. DerSimonian–Laird random-effects model was used for meta-analysis of effect size. The $P < .05$ (2 tailed) was considered statistically significant for computed effects. We examined the publication bias at the outcome level with Begg funnel plot. We used Jadad scale[18] to assess the quality of studies. Jadad scale has a score of 0 to 5 based on the basis of randomization, blinding, and attrition of participants. Study heterogeneity was evaluated with Cochran Q and I^2 index with $P < .10$ and I^2 of >60% considered significant heterogeneity, which was explored with sensitivity analysis. Statistical analyses were performed with Comprehensive Meta-Analysis (CMA 2.2; Biostat, Englewood, NJ, USA) and Review Manager (RevMan 5.2; Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark).