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Original Contribution

Using real-world data to assess changes in low-density lipoprotein cholesterol and predicted cardiovascular risk after ezetimibe discontinuation after the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial

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Dyslipidemia;
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BACKGROUND: The 2008 Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study demonstrated ezetimibe + simvastatin vs simvastatin alone had a neutral effect on the surrogate endpoint of carotid intima-media thickness. Subsequent media portrayal of the study prompted ezetimibe discontinuation in many patients.

OBJECTIVE: The objective of the study was to assess impact of ENHANCE reporting on ezetimibe discontinuation, low-density lipoprotein cholesterol (LDL-C) changes, and potential cardiovascular disease (CVD) risk.

METHODS: This analysis used claims data in a retrospective, observational study of patients receiving ezetimibe + statin and compared LDL-C for patients who discontinued ezetimibe (n = 970) vs those who continued ezetimibe + statins (n = 3706) after ENHANCE results disclosure. Change in relative CVD risk was estimated from the absolute LDL-C difference between groups per the Cholesterol Treatment Trialists' meta-analysis of statin trials.

RESULTS: The rate of ezetimibe discontinuation was 2% in the 6 months before and 21% in the 6 months after reporting of ENHANCE results. Among patients who ultimately discontinued vs continued ezetimibe, respective mean LDL-C levels were 79.8 and 78.3 mg/dL 6 months before

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reporting of the ENHANCE results and 93.5 and 78.1 mg/dL 6 months after reporting of ENHANCE. Predictive application of the Cholesterol Treatment Trialists' meta-analysis suggested the 13.9 mg/dL increase in mean LDL-C translated to a 9.4% increase in relative CVD risk for those who discontinued ezetimibe.

CONCLUSION: After reporting of the neutral ENHANCE results, ezetimibe discontinuation rate increased, LDL-C levels increased, and predicted CVD risk increased among those who discontinued ezetimibe. Characterization of clinical outcomes regarding lipid-altering agents based on surrogate biomarker studies not designed to assess CVD outcomes may be misleading, potentially placing patients at increased CVD risk.

Introduction

Biomarkers and surrogate endpoints are often evaluated in clinical trials to assess the efficacy of lipid-altering therapeutic interventions.[1,2] Beginning in the 1980s, during early statin development, clinical trials often began by assessing the safety and efficacy of statins in reducing low-density lipoprotein cholesterol (LDL-C) levels. Because LDL-C was the main biomarker recognized by the US Food and Drug Administration, such an approach was consistent with meeting regulatory requirements necessary for approval of statin therapy to improve lipid levels (eg, indicated use to reduce LDL-C levels among patients with dyslipidemia).[3,4] Years later, after clinical outcome studies demonstrated a reduction in atherosclerotic cardiovascular disease (ASCVD) events, many statins subsequently received an additional regulatory indication to reduce ASCVD events.

Interim imaging studies were frequently undertaken in clinical development programs to evaluate the effect of lipid-altering agents on the surrogate of carotid intima-media thickness (CIMT), as they could be completed in a timelier manner than ASCVD outcomes studies.[5] The underlying assumption was that if the IMT of the carotid arteries was decreased, the same would apply to cardiac atheroma. However, CIMT reduction was not found to be consistently correlated with ASCVD risk reduction in statin clinical trials. One potential reason was that the greater use of statin therapy not only reduced atheroma volume, but also "stabilized" atherosclerotic plaques via reduced inflammation and increased collagen content,[6] thus contributing to a lower baseline CIMT over time[7,8] and greater challenges in producing differential CIMT and ASCVD outcomes benefits.

For example, in trials using atorvastatin up to 80 mg/d, CIMT was often minimal, mitigating the potential of a lipid-altering agent to demonstrate a differential response of active treatment vs placebo.[9–11] The results of these CIMT trials contrasted with the known benefits of atorvastatin demonstrated in cardiovascular outcome trials, including those in which patients were previously treated with lipid-lowering therapy.[12] This suggests that the potential clinical value of surrogate CIMT study results are dependent on a number of factors (eg, baseline CIMT) and should not necessarily be relied on for predicting clinical outcomes. The best evidence to assess ASCVD outcomes of a lipid-altering agent is via the results of ASCVD outcomes trials.

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study was a CIMT study conducted in patients with familial hypercholesterolemia.[13] This study demonstrated greater reductions in mean LDL-C levels with ezetimibe plus simvastatin compared with simvastatin monotherapy, supporting results of previous studies on the lipid-lowering effects of ezetimibe.[14,15] However, possibly because of widespread use of statin therapy in patients before ENHANCE enrollment and the minimal CIMT found at baseline, ENHANCE demonstrated no improvement in CIMT for ezetimibe and simvastatin vs simvastatin alone.[13] Reporting of the trial results on January 14, 2008, resulted in a portrayal of the ENHANCE trial by the media that called into question the clinical benefit of ezetimibe as interpreted by some investigators.[16–18] Based on the results of the ENHANCE study, some recommended other lipid-altering agents, such as niacin and fibrates, as preferred add-on therapies to statins.[18] Consequently, many patients discontinued ezetimibe therapy. Ezetimibe's decreased use in combination with statins was estimated to lead to increased LDL-C levels, as well as a reduction in the proportion of patients achieving optimal LDL-C treatment goals, potentially increasing ASCVD risk in these patients.[19–21] The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial, an ASCVD outcome study, ultimately demonstrated that the combination of simvastatin plus ezetimibe therapy produced greater reductions in LDL-C levels for patients with acute coronary syndrome compared with simvastatin alone.[22] Most importantly, the combination of ezetimibe plus statin produced a statistically significant reduction in ASCVD events vs statin monotherapy.[22]

This report examines the frequency of ezetimibe use before and after the reporting of the ENHANCE results, using a claims database that included LDL-C values. The study objectives were to assess discontinuation rates for ezetimibe-containing treatment regimens after the report of