Ezetimibe and Statins - An Overview of ACC 2016

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Abstract:

In this review we study the efficacy and safety of ezetimibe-statins combination therapy in comparison to statin monotherapy in terms of the prevention of cardiovascular diseases. This review summarizes the most current clinical data available on the lipid-altering efficacy and safety of ezetimibe co-administered with statins in patients with hypercholesterolemia and in other diverse populations. Further cholesterol lowering with ezetimibe will also result in a reduction of myocardial ischemia during daily life. The addition of ezetimibe (EZ) to ongoing statin therapy provides additional clinical benefit with respect to CVD outcomes. The objective of this review is to assess the economic value of ezetimibe (EZ) in patients with CVD in the US healthcare system accounting for the impending change in cost due to patent expiry. Patients with acute coronary syndrome (ACS) vary in their risk for recurrent CV events. Risk assessment may be useful to identify patients who have the greatest potential for benefit from the addition of EZ to statin therapy. It has been still important to identify a promising anti-atherosclerotic pharmacologic strategy to reduce “residual risk” of cardiovascular events.

Keywords: Ezetimibe, Statins, CAD, LDL-C, CVD

Introduction:

Cholesterol lowering is associated with a reduction in cardiovascular morbidity and mortality. Statins are the main drugs for cholesterol lowering. Ezetimibe (EZ) when added to statins gives further reduction in cholesterol but its long-term effect on cardiovascular morbidity and mortality and ischemic events is not known.¹ In patients with established Coronary artery disease (CAD) or atherosclerosis in other vascular beds, or in patients at high risk of developing CAD, lowering serum total and low-density lipoprotein cholesterol (LDL-C) has been associated with a reduction in cardiovascular morbidity and mortality, and total mortality. Ezetimibe is a selective inhibitor of intestinal cholesterol absorption that results in an additional 15% to 25% reduction of LDL-C. Ezetimibe is suggested for patients who do not reach recommended LDL-C targets on an optimal dosage of statins alone. A recent and more effective therapeutic hypcholesterolemic strategy is to treat the two main sources of cholesterol simultaneously.
(production of cholesterol, mainly in the liver, and absorption of cholesterol in the intestine) with a complementary mechanism of action, by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, with a statin, which inhibits cholesterol production in the liver. Ezetimibe (EZ) is safe and effective for 2° prevention with an overall 10% relative reduction in CV death, myocardial infarction or ischemic stroke (CVD/MI/iCVA).

Effect of Ezetimibe and Statins in Myocardial Ischemia

In this study 50 patients with proven stable coronary artery disease (CAD) and at least one episode of ST-segment depression on ambulatory ECG monitoring. All of them were receiving optimal therapy for CAD including statin therapy for cholesterol reduction. 25 patients were randomized to continue their statin therapy (Statin only group) and 25 to receive statin plus Ezetimibe 10mg/day (ezetimibe group). Serum cholesterol and LDL cholesterol levels and ambulatory monitoring were repeated after 4 to 6 months of therapy. The two groups were comparable with respect to baseline characteristics, number of episodes of ST-segment depression, and baseline serum cholesterol levels.\(^1\)

Result of this study shows that the ezetimibe group had lower mean total and LDL cholesterol levels at study end and experienced a significant reduction in the number of episodes of ST-segment depression compared with the statin only group. ST-segment depression was completely resolved in 13 of 25 patients (52%) in the ezetimibe group versus 3 of 25 (12%) in the statin only group. The ezetimibe group exhibited a highly significant reduction in ambulatory ischemia (P<.001). By logistic regression, treatment with ezetimibe was an independent predictor of ischemia resolution.\(^1\)

Ezetimibe and Statins as Anti- Atherosclerotic strategy

The PRECISE-IVUS (Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound) trial was a prospective, randomized, controlled, multicenter study. The eligible patients undergoing IVUS-guided percutaneous coronary intervention (PCI) was randomly assigned to receive either atorvastatin alone or atorvastatin plus ezetimibe (10mg) daily. The dosage of atorvastatin was uptitrated with a treatment goal of lowering low-density lipoprotein cholesterol (LDL-C)<70mg/dL. Serial volumetric IVUS was performed at baseline and 9-12 months follow-up to quantify the coronary plaque response in 202 patients.

Result of this study shows that the combination of ezetimibe/atorvastatin resulted in lower levels of LDL-C than the atorvastatin monotherapy (63.2±;16.3mg/dL vs. 73.3±;20.3mg/dL, p<0.001). The absolute change in percent atheroma volume (PAV) was more beneficial in the ezetimibe/atorvastatin than in the atorvastatin alone (-1.4% [-3.4% to -0.1%] vs. -0.3% [-1.9% to 0.9%],p=0.001). For PAV, a significantly greater percentage of patients with ezetimibe/atorvastatin showed coronary plaque regression (78% vs. 58% in the atorvastatin monotherapy, p=0.004). Both strategies had a low incidence of laboratory abnormalities and
cardiovascular events. Furthermore, contrary to the patients without statin pretreatment (-1.3 [-3.1 to -0.1]% vs. -0.9 [-2.3 to 0.9], p=0.12), the ezetimibe/atorvastatin combination showed the significantly stronger reduction in ΔPAV, compared with atorvastatin alone, in patients with statin pretreatment (-1.8 [-3.6 to -0.3]% vs. -0.1 [-1.6 to 0.8], p=0.002).\(^4\)

**Ezetimibe and Statins: Atherothrombotic Risk Stratification**

A simple 9-point risk stratification tool was previously derived and validated in a large population with atherothrombosis (TRA 2°P-TIMI 50). This study applies this tool prospectively to 17,717 pts stabilized post-ACS randomized to EZ/simvastatin (S) or S alone in IMPROVE-IT. Efficacy was assessed by baseline risk for CVD/MI/iCVA.

**Result of this study shows** that all clinical variables were validated as independent risk indicators (RI) of CVD/MI/iCVA (p<0.001). The integer-based scheme showed a strong graded relationship with the rate of CVD/MI/iCVA and the components (p-trend<0.0001 for all). Intermediate-risk pts (RI=2; 29% of events) had a 2.2% absolute risk reduction (ARR) in CVD/MI/iCVA at 7 yrs with EZ/S compared to S alone and high-risk (RI≥3; 42% of events) had a 6.2% ARR, translating to a number-needed-to-treat of 46 and 16, respectively. Evaluation of individual endpoints showed significant ARR in the high-risk pts of 6.0% (2.8, 9.2) for MI and 2.4% (0.4, 4.4) for iCVA.\(^3\)

**Clinical benefits of Ezetimibe with Statins in Cardiovascular Disease (CVD) IMPROVE-IT STUDY**

In this IMPROVE-IT Study Markov model with annual cycles to project the long term cost and benefits of EZ add-on to statin therapy in patients with a history of CVD and LDL-C values >=70 mg/dl. Baseline risk of CVD events were derived from the placebo arm of the IMPROVE-IT study and risk reduction in CVD events was based upon the relationship between LDL changes and reduction in CV events from CTT meta-analysis. Health state cost, utilities values were taken from recent published assessments of statins in the US and Non-CVD death rates were based on US mortality statistics. An appropriate cohort of statin patients was identified from the IMS Pharmetrics and EMR databases. This study conducted an evaluation where the price of EZ was fixed at the current wholesale acquisition cost (WAC) for the first year and the price of EZ was reduced by 90% after one year of therapy.

**Result of this study involves** 548 statin patients in the IMS database between the ages of 35-75 with a history of CVD and LDL-C >=70 mg/dl. Patients had a mean age of 58 years, average baseline LDL-C of 94.6 mg/dl, 55.5% were male and 35.6% of patients had diabetes. Based on a reduction in current WAC price ($7.74) of 90% after 1 year analysis resulted in an additional $1491 in cost and a gain of 0.18 life years, for an additional $8,387 per QALY gained.
Incremental reduction in event cost due to the addition of EZ offset almost 80% of the incremental total drug cost of statin plus EZ.5

Conclusions: When statins are given with ezetimibe it can result in reduction or resolution of myocardial ischemia recorded as episodes of ST-segment depression in ambulatory monitoring of the ECG. Atherothrombotic risk stratification identifies high-risk patients who derive greatest benefit from the addition of EZ for 2° prevention after ACS. As compared with statin monotherapy, the dual lipid-lowering with ezetimibe/atorvastatin showed greater coronary plaque regression, which might be attributed to cholesterol absorption inhibition-induced aggressive lipid-lowering. With the positive result of IMPROVE-IT and impending ezetimibe patent expiry, these results suggest that initiating add-on therapy with EZ is a clinical and cost-effective option for CVD patients treated with statins.

References: