Journal of Clinical Lipidology (2016) 10, 1379–1388

Journal of Clinical Lipidology

Model-observational bridging study on the effectiveness of ezetimibe on cardiovascular morbidity and mortality in France: A population-based study

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KEYWORDS:
Cardiovascular disease;
Cohort;
Lipid-modifying drugs;
Prevention;
Hypercholesterolemia

BACKGROUND: To evaluate the real-life impact of ezetimibe on cardiovascular (CV) morbidity and mortality in France.

OBJECTIVE: To estimate the number of non-fatal and fatal CV events that could be prevented and corresponding number of patients needed to treat (NNT) with ezetimibe to prevent one CV event over 5 years.

METHODS: Non-interventional 48-month follow-up cohort conducted in hypercholesterolemic patients starting on ezetimibe <3 months at study entry, either as monotherapy or combined with statins. Prediction modeling using discrete event simulation with calibrated Framingham CV risk equations was applied to data from pivotal clinical trials on ezetimibe and real-life data derived from the cohort.

RESULTS: A total of 3215 patients in the cohort accumulated 9314 person-years of follow-up for an average of 2.9 years. Mean age was 61.5 (standard deviation [SD] = 10.7), 54.6% were males, and 27.0% had a history of CV disease. Baseline LDL-cholesterol averaged 4.1 mmol/L (159 mg/dL; SD = 1.0) and HDL-C 1.6 mmol/L (62 mg/dL; SD = 0.5). LDL-C decreased in the first 12 months in ezetimibe-LLT (lipid-lowering therapy) initiators, switchers (monotherapy), and combination

The EZE study was funded by MSD France and was conducted by LASER under the supervision of an independent scientific board, the members of which take responsibility as co-authors of the present manuscript. MSD France was admitted as an observer to the scientific committee meetings regarding the design of the study protocol, statistical analysis plan, progress reports and final report. The sponsor took no part in coordinating the study, its conduct, data collection or analyses, and was not informed of who participated as investigators.

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Submitted March 29, 2016. Accepted for publication August 27, 2016.

http://dx.doi.org/10.1016/j.jacl.2016.08.015

therapy with a statin by respectively 21.3%, 6.4%, and 29.1%. The corresponding predicted rate reductions of CV events (non-fatal and fatal) compared to no treatment or to a statin (combination therapy) were respectively 8, 2, and 12 per 1000 patients treated over 5 years, with a global NNT of 143 patients over 5 years.

CONCLUSION: These results, accounting for observed CV event rates, risk factors evolution over time and adherence to treatment in real life, were consistent with those from clinical trials.

Introduction

Mortality from cardiovascular (CV) disease is declining across most European countries but remains the leading cause of death in women and the second in men in France.[1] CV disease is multifactorial in its causation, and elevated blood cholesterol is one of the major risk factors for both nonfatal and fatal CV events in people with and without a history of CV diseases.[2] Lowering plasma LDL-C reduces CV risk in primary as well as in secondary prevention of CV events.[3,4] Consequently, European and French guidelines recommend lipid-modifying treatments for patients with dyslipidemia at moderate-to-high cardiovascular risk.[5] Although statins are the first-line therapy, ezetimibe is a medication currently approved in France as monotherapy for patients in whom statins are contraindicated or are intolerant to statins, and in addition to a statin for patients with hypercholesterolemia not controlled by a statin alone.[6] At the time this recommendation was made, French authorities had requested from the manufacturer a long-term, real-life study on the health impact of ezetimibe on CV morbidity and mortality projected over the entire adult French population. The EZE cohort and the Model Observational Bridging Study (MOBS) were undertaken to address this request. The objective of the EZE-MOBS study was to estimate the number of nonfatal and fatal CV events that could be prevented by ezetimibe and the corresponding number of patients needed to treat (NNT), accounting for the real pattern of utilization and patients' adherence to therapy in France, as well as for changing CV risk factors over time.

Methods

The EZE cohort

The EZE cohort was created to provide real-life data on the evolution of CV risk factors in patients with hypercholesterolemia who had one of the following indications for ezetimibe: statin contra-indication, statin intolerance, or statin lack of efficacy. Recruitment of patients was prospective and naturalistic establishing as only inclusion criteria a first lifetime treatment with ezetimibe for a duration of no more than three months before inclusion as it occurs in real clinical practice. No information was provided to recruiting physicians on ezetimibe indications, and exposure was classified *a posteriori* for the analyses in three groups: monotherapy (ATC code C10AX09) at the time of initiating lipids-lowering therapy (LLT), monotherapy as a switch from another LLT, and combination therapy with a statin (free association ATC code C10A1 or fixed association to simvastatin ATC code C10BA02).

Study population

The cohort was designed to represent the population of France by using a physician recruitment campaign that randomized lists of general practitioners (GPs) and cardiologists (outpatient clinics) at a ratio of 9:1 from the national physician registry. Between November 2008 and July 2010, participating physicians invited all consecutive eligible adult patients (≥18 years) who understood French, were likely to be followed up for at least 6 months and were not included in any clinical trial, to participate in the cohort. Follow-up of the EZE cohort lasted until July 2012 to ensure collection of data over at least 24 months for the last patients included.

Cardiovascular risk factors and follow-up

At inclusion, physicians completed a standardized baseline questionnaire collecting information on personal and family history of CV disorders, lifestyle and medical CV risk factors, current medications, and blood lipid measurements, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides for each patient. Monitoring of blood lipids and other CV risk factors was performed yearly thereafter. Patients were interviewed by a trained interviewer via telephone at 6, 18, 30, and 42 months using a methodology that had been previously validated.[7] Information collected included any change in CV risk factors and utilization of CV medication according to 3 drug groups: antihypertensive, antiplatelet/anticoagulant, and antidiabetic drugs. Detailed utilization of ezetimibe, treatment adherence, and interruption was collected at each interview. In the event that the patient did not attend a follow-up medical visit, additional telephone interviews were scheduled with the patient to ensure continuity of follow-up.