International Journal of Cardiology 167 (2013) 225–231

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Lipid-altering efficacy and safety profile of co-administered extended release niacin/laropiprant and simvastatin versus atorvastatin in patients with mixed hyperlipidemia

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ARTICLE INFO

Article history:
Received 13 September 2011
Accepted 20 December 2011
Available online 4 February 2012

Keywords:
Statin
Mixed hyperlipidemia
Lipoproteins
Niacin
Laropiprant

ABSTRACT

Background: Extended-release niacin/laropiprant (ERN/LRPT) reduces flushing and preserves the lipid-modifying effects of ERN. This study compared the efficacy and safety of ERN/LRPT plus simvastatin (ERN/LRPT + SIMVA) with atorvastatin (ATORVA) in patients with mixed hyperlipidemia.

Methods: After a 4-week placebo run-in, 2340 patients (LDL-C ≥130 and ≤190 mg/dL, TG ≥150 and ≤500 mg/dL and above NCEP ATP III risk-based LDL-C goal) were randomized to 1 of 6 treatment arms: ERN/LRPT 1 g/20 mg + SIMVA (10 or 20 mg), or ATORVA (10, 20, 40, or 80 mg) once daily.

Results: At Week 12, ERN/LRPT + SIMVA was superior to ATORVA in decreasing LDL-C/HDL-C (primary endpoint) at each pre-specified dose comparison: ERN/LRPT + SIMVA 20 mg vs. ATORVA 10 mg (−13.2%; $p<0.001$); ERN/LRPT + SIMVA 40 mg vs. ATORVA 20 mg (−10.8%; $p<0.001$); ATORVA 40 mg (−5.1%; $p<0.001$); and ATORVA 80 mg (−4.2%; $p=0.007$). At Week 12, ERN/LRPT + SIMVA was superior to ATORVA in increasing HDL-C and reducing TG for all pre-specified treatment comparisons, and reducing non-HDL-C and LDL-C for the ERN/LRPT + SIMVA 20 mg versus ATORVA 10 mg and ERN/LRPT + SIMVA 40 mg versus ATORVA 20-mg dose comparisons, but not the ERN/LRPT + SIMVA 40 mg versus ATORVA 40- and 80-mg dose comparisons. Adverse experiences (AEs) typically associated with niacin (flushing, pruritus, increased glucose, increased uric acid) were more common with ERN/LRPT + SIMVA, and hepatic-related laboratory AEs were more common with ATORVA.

Conclusion: ERN/LRPT + SIMVA was generally superior to ATORVA in improving lipid parameters after 12 weeks and was generally well tolerated in patients with mixed hyperlipidemia.

1. Introduction

Mixed hyperlipidemia is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C). The successful treatment of mixed hyperlipidemia remains an unmet medical need. Whereas statin drugs provide excellent LDL-C- and TG-lowering effects and reduce cardiovascular risk, they have only modest efficacy on raising HDL-C. Extended-release niacin (ERN) reduces LDL-C and TG levels, is the most effective agent for raising HDL-C, and attenuates the risk of cardiovascular disease [1–6]. Coadministration of ERN with a statin offers the potential for comprehensive lipid management and additional cardiovascular risk reduction; however, its use has been hampered by niacin-induced flushing, mediated primarily by prostaglandin D2 (PGD2) [7]. Laropiprant (LRPT) is a potent, once-daily, highly selective PGD2 receptor (DP1) antagonist [8]. A combination tablet containing ERN and LRPT (ERN/LRPT) offers the beneficial lipid-altering effects of ERN with improved tolerability [9,10]. A previous Phase III, factorial study demonstrated that ERN/LRPT coadministered with simvastatin (ERN/LRPT + SIMVA) significantly improved the overall lipid profile compared with ERN/LRPT or SIMVA alone, and was generally well tolerated in patients with mixed hyperlipidemia [11]. The present study evaluated the efficacy and safety of ERN/LRPT + SIMVA compared with atorvastatin (ATORVA) in patients with mixed hyperlipidemia.

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0167-5273/$ – see front matter © 2011 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ijcard.2011.12.103

2. Patients and methods

2.1. Patient selection criteria

This study enrolled men and women ages 18 to 80 years with mixed hyperlipidemia (LDL-C between 130 and 190 mg/dL and TG between 150 and 500 mg/dL after washout from lipid-modifying therapies), not at NCEP ATP III risk-based LDL-C goal [1]. All patients provided written informed consent to participate in this study. High-risk patients (CHD/CHD risk equivalent) being treated with a statin were not eligible as wash-out of the statin would have been required. Investigators were asked to determine and record a patient's baseline glycemic status as normal, impaired (fasting serum glucose [FSG] ≥20 mg/dL), or diabetic (based on their own medical judgment or by the patient's primary physician).

Patients were excluded if they had the following laboratory values at Visit 1: creatinine >2.0 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5× upper limit of normal (ULN), creatine kinase (CK) >2× ULN, or an abnormal thyroid stimulating hormone. Prohibited medical conditions included endocrine/metabolic diseases affecting lipids/lipoproteins, clinically significant renal disease, cardiovascular event or procedure within 3 months of study visit 1, active or chronic hepatic disease, peptic ulcer disease within 3 months of visit 1, episode of gout within 1 year of visit 1, unless on allopurinol, a history (≤5 years) of malignancy, partial ileal/gastric bypass surgery, and HIV. Women who were pregnant or expecting to become pregnant or breast-feeding were excluded from the study. Patients taking lipid-altering agents, potent CYP3A4 inhibitors, or drugs increasing myopathy risk, systemic corticosteroids, or anabolic steroids, cyclical hormonal contraceptives, or intermittent hormone replacement therapies, or high doses of antioxidant vitamins were excluded.

2.2. Study design

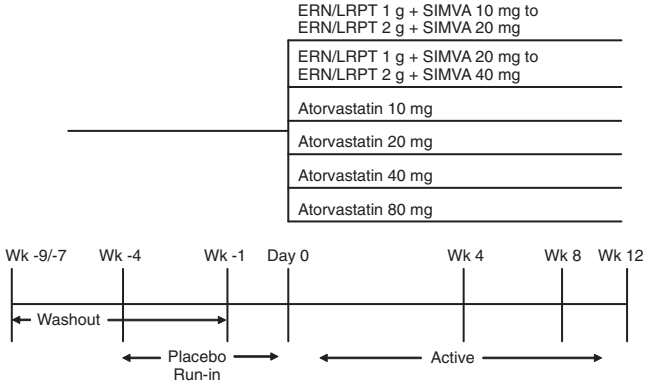
This was a randomized, double-blind, multi-center study conducted at 265 sites in 14 countries. Following a washout period of lipid-modifying therapies (if needed) and a concurrent 4-week placebo run-in period, eligible patients were randomized in a 2:3:2:3:3:3 allocation ratio to 1 of 6 treatment arms: ERN/LRPT 2 g/40 mg + SIMVA (20 or 40 mg), or ATORVA (10, 20, 40, or 80 mg) once daily. ERN/LRPT was titrated beginning with 1 g and doubled to 2 g after 4 weeks; SIMVA was titrated from 20 mg to 40 mg (Fig. 1). Patients were centrally randomized via Interactive Voice Response System.

There were six scheduled clinic visits at Weeks −4, −1, Day 0, and Weeks 4, 8, and 12. The final visit was followed 14 days later by a post-study telephone contact to assess for potential serious adverse experiences. Patients who discontinued their participation in the study prior to completion were followed and contacted at their intended Week 12 visit date to assess for potential serious cardiovascular adverse experiences and all-cause mortality.

The study protocol was reviewed and approved by the appropriate ethics committees/institutional review boards. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

2.3. Efficacy assessments

The primary efficacy endpoint was the percent change from baseline in LDL-C:HDL-C ratio following 12 weeks of active treatment. Key secondary efficacy endpoints included the percent change from baseline in HDL-C, TG, non-HDL-C, and LDL-C. Additional efficacy endpoints included the percent change from baseline in apolipoprotein (Apo) B, Apo A-1, lipoprotein (a) [Lp(a)], total cholesterol (TC), and C-reactive protein (CRP). The following four dose comparisons were pre-specified:



ERN/LRPT 1 g = ERN 1 g/LRPT 20 mg; ERN/LRPT 2 g = ERN 2 g/LRPT 40 mg

Fig. 1. Study design.

ERN/LRPT 2 g/40 mg + SIMVA 20 mg vs. ATORVA 10 mg;
ERN/LRPT 2 g/40 mg + SIMVA 40 mg vs. ATORVA 20 mg;
ERN/LRPT 2 g/40 mg + SIMVA 40 mg vs. ATORVA 40 mg; and
ERN/LRPT 2 g/40 mg + SIMVA 40 mg vs. ATORVA 80 mg.

2.4. Safety and tolerability assessments

Safety and tolerability were evaluated throughout the study. Assessments included adverse experiences, physical examinations, laboratory tests, electrocardiograms and vital signs. Laboratory evaluations included serum ALT, AST, CK, FSG, and other general surveillance labs (hematology, chemistry, urinalysis, beta-human chorionic gonadotropin).

The following laboratory abnormalities were prespecified as conditions for discontinuation: consecutive ALT or AST elevations ≥3× ULN; consecutive CK elevations ≥5× and <10× ULN with muscle symptoms, consecutive CK elevations ≥10× ULN with or without muscle symptoms, or single CK elevations ≥20× ULN with or without muscle symptoms; TG levels >600 mg/dL on repeat measure; and positive pregnancy test. Pre-specified discontinuation was also defined for patients who experienced hypersensitivity or severe intolerance to study therapy or who required continuous treatment with systemic corticosteroids. Serious cardiovascular events and any deaths occurring during the study and follow-up period were subject to adjudication by an independent adjudication committee.

2.5. Statistical methods

The change from baseline in the LDL-C:HDL-C ratio was assessed by comparing mean percentage changes at Week 12 for ERN/LRPT 2 g + SIMVA 20 mg vs. ATORVA 10 mg, ERN/LRPT 2 g + SIMVA 40 mg vs. ATORVA 20 mg; ATORVA 40 mg; and ATORVA 80 mg using a parametric analysis of covariance (ANCOVA) model, with factors for baseline LDL-C stratum (≥130 to <160 mg/dL and ≥160 to ≤190 mg/dL), baseline TG stratum (≥150 to <250 mg/dL and ≥250 to ≤500 mg/dL), baseline LDL-C:HDL-C, gender, cohort of patients (i.e., the 1st cohort of 1770 randomized in US sites or the 2nd cohort of 565 randomized in non-US sites), and treatment group. Treatment group comparisons were performed using the appropriate contrasts from the ANCOVA model.

The comparisons in percent change from baseline in HDL-C and non-HDL-C were assessed using the similar ANCOVA model for LDL-C/HDL-C, with respective baseline HDL-C and baseline non-HDL-C instead. The percentage change from baseline in LDL-C was assessed using the ANCOVA model, with factors for baseline TG stratum (≥150 to <250 mg/dL and ≥250 to ≤500 mg/dL), baseline LDL-C, gender, and treatment group. The percentage change from baseline in TG was analyzed using the ANCOVA model above applied to Tukey's normalized scores of the percentage change in TG, including factors for baseline LDL-C stratum (≥130 to <160 mg/dL and ≥160 to ≤190 mg/dL), normalized scores of baseline TG, gender, cohort of patients (i.e. the 1st cohort of 1770 randomized in US sites or the 2nd cohort of 565 randomized in non-US sites), and treatment group. The between-treatment group differences in medians were assessed using Hodges–Lehman estimates, with the corresponding distribution-free 95% CI based on Wilcoxon's rank sum test.

A closed ordered testing procedure was applied to the primary and key secondary efficacy endpoints to adjust for multiplicity and to control the overall α level across the tests at $\alpha = 0.050$. Specifically, the testing order was LDL-C/HDL-C, HDL-C, TG, non-HDL-C, and LDL-C among the primary and key secondary efficacy endpoints. Moreover, the closed ordered testing procedure was applied for four dose comparisons in the following order: ERN/LRPT 2 g + SIMVA 20 mg vs. ATORVA 10 mg, ERN/LRPT 2 g + SIMVA 40 mg vs. ATORVA 20 mg, ERN/LRPT 2 g + SIMVA 40 mg vs. ATORVA 40 mg, and ERN/LRPT 2 g + SIMVA 40 mg vs. ATORVA 80 mg within each of endpoints above. If the first comparison in the endpoint with higher order was significant at $\alpha = 0.050$, testing of next endpoint would be performed.

Safety and tolerability were assessed by a statistical and clinical review of all safety parameters. Statistical tests were performed and the 95% CI and p-values were displayed on the prespecified safety parameters of interest, including hepatitis-related adverse experiences (AEs), ALT and/or AST elevations ≥3× ULN consecutive, ≥5× ULN, ≥10× ULN, CK elevations ≥10× ULN, CK elevations ≥10× ULN with muscle symptoms or with drug-related muscle symptoms, confirmed adjudicated cardiovascular AEs, new diagnosis of impaired fasting glucose ([IFG], identified by a pre-defined set of MedDRA terms) and new onset diabetes defined as having experienced an AE related to a diagnosis of diabetes (based on a pre-defined set of MedDRA terms), or if an anti-diabetic medication was initiated during the course of the study.

For other clinical and laboratory AEs, events were listed and summarized by frequency of occurrence, and the counts and percentages were tabulated by treatment group. The between-group pairwise comparisons were performed using Fisher's exact test. Ninety-five percent CIs of between-treatment differences in percentages were derived using Wilson's score method. Vital signs and selected laboratory tests were also summarized.

3. Results

3.1. Patient accounting and baseline characteristics

A total of 11 871 patients were screened, of which 9531 were excluded and 2340 were randomized. The majority of patients were