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Efficacy and safety of combination therapy with niacin extended-release and simvastatin versus atorvastatin in patients with dyslipidemia: The SUPREME Study

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BACKGROUND: Aggressive treatment of low-density lipoprotein cholesterol (LDL-C) fails to prevent most cardiovascular (CV) events. Concurrent treatment of LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) should be considered in patients with dyslipidemia.

OBJECTIVE: The efficacy and safety of a proprietary niacin extended-release and simvastatin (NER/S) combination were compared to atorvastatin monotherapy in a multicenter, Prospective, Randomized (3:2), Open-label, Blinded Endpoint (PROBE) study.

METHODS: Following ≥4 weeks without lipid-modifying therapies, 193 patients with dyslipidemia were treated with NER/S (n = 114; 1000/40 mg/day, weeks 1 to 4; 2000/40 mg/day weeks 5 to 12) or atorvastatin (n = 79; 40 mg/day, weeks 1 to 12).

RESULTS: Compared to atorvastatin, NER/S had a larger beneficial effect on HDL-C (primary end point: 30.1 ± 2.3% and 9.4 ± 2.6%, respectively; $P < .001$), TG ($P = .02$), and lipoprotein(a) (Lp[a]; $P < .001$), and similar effects on LDL-C and non–HDL-C. Two-thirds of patients treated with NER/S concurrently attained LDL-C (CV risk-adjusted goals), HDL-C (≥40 mg/dL), and TG (<150 mg/dL) targets, compared to one-third of patients treated with atorvastatin ($P < .001$). Flushing was the most common treatment-emergent adverse event (TEAE) (67.5% NER/S and 10.1% atorvastatin; $P < .001$). Seventy-five percent of flushing episodes were mild to moderate. More patients treated with NER/S discontinued due to TEAEs (21.1% and 3.8%; $P < .001$); the most common TEAE was flushing.

CONCLUSION: Compared to atorvastatin, NER/S provided superior improvements in HDL-C, TG, and Lp(a) and comparable improvements in non–HDL-C and LDL-C. Treatment with NER/S should be considered for patients with dyslipidemia requiring comprehensive lipid control.

Treatment guidelines for patients with dyslipidemia recommend reducing low-density lipoprotein cholesterol (LDL-C) to <100 mg/dL and non–high-density lipoprotein cholesterol (non–HDL-C; specific for patients with triglycerides [TG] >200 mg/dL) to <130 mg/dL in patients with coronary heart disease (CHD) or its risk equivalent.[1] Unfortunately, even with low levels of LDL-C achieved with statin monotherapy (from clinical trials lasting 4 to 5 years), the risk of cardiovascular (CV) events has only been reduced by approximately 30%.[2,3] A growing body of evidence has

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identified high-density lipoprotein cholesterol (HDL-C),[4–7] TG,[8,9] and lipoprotein(a) (Lp[a])[10,11] as independent factors predictive of CV risk. Although treatment guidelines have not defined a target level for HDL-C, increased HDL-C has been determined to result in reduced CV risk in patients receiving statin therapy, even those with LDL-C <70 mg/dL.[5]

To help meet the therapeutic needs of patients with dyslipidemia, a tablet combining a proprietary niacin extended-release (NER; Niaspan, Abbott, Abbott Park, IL) core-coated with simvastatin (NER/S, Simcor, Abbott) was recently developed. Statins are the most effective agents available for decreasing LDL-C,[2,12] whereas niacin is the most potent agent available for increasing HDL-C. Although the benefit of lowering TG and Lp(a) remains to be established, niacin has been shown to lower TG, Lp(a), LDL-C, and non–HDL-C, factors believed to be associated with increased CV risk.[13–15] Both simvastatin and niacin have well-established clinical benefits (outcomes data) and a long history of safety and tolerability.[3,16–18] In previous clinical trials, treatment with NER/S compared to simvastatin monotherapy demonstrated significant improvements in nearly all lipid parameters in patients with dyslipidemia and a safety profile consistent with NER and simvastatin monotherapies.[19–22]

The objectives of the SUPREME study were to compare the efficacy and safety of once-daily NER/S 2000/40 mg/day, after rapid titration, to atorvastatin 40 mg/day in patients with dyslipidemia who were either treatment-naïve or who had been free from lipid-modifying therapy for ≥4 weeks.

Methods

Study design

The Study to Compare the Lipid Effects of Niacin ER and Simvastatin to Atorvastatin in Subjects with Hyperlipidemia or Mixed Dyslipidemia (the SUPREME study; ClinicalTrials.gov Identifier NCT00465088) was a phase IIIB, 12-week, multicenter, Prospective, Randomized, Open-label, Blinded Endpoint (PROBE) design performed in the United States.

SUPREME consisted of two phases: a screening phase and a treatment phase. The study was designed and monitored in accordance with the ethical principles of good clinical practice, as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. The institutional review board for each study site approved the study protocol, and all participants provided written informed consent before enrollment.

Main inclusion criteria

Patients included men and women ≥21 years of age, with dyslipidemia, defined as LDL-C ≥130 and <250 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and TG <350 mg/dL. Women could not be pregnant, breastfeeding, or planning to conceive or breastfeed. Patients had to reasonably comply with the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Therapeutic Lifestyle Changes (TLC) diet for a minimum of 4 weeks during the screening period and be willing to maintain compliance with this diet throughout the study.[23] Patients taking antidyslipidemic medications were required to discontinue them at least 4 weeks before randomization. Therapies known to have minor effects on serum lipids, including thiazide diuretics, systemic β blockers, psyllium products, plant stanols, plant sterols, omega-3 fatty acids, fish oils, and soluble fiber were permitted provided that dosages of these agents were stable during screening and throughout the study. Thyroid and estrogen replacement therapy were allowed if the dosage was stable within 3 months from the start of the study through its completion.

Main exclusion criteria

Exclusion criteria included an allergy, hypersensitivity, or intolerance to niacin (unable to tolerate daily niacin therapy due to adverse events), statins, or their derivatives; excessive alcohol consumption or a history of substance abuse within 12 months of screening; use of an investigational study medication or participation in an investigational study within 30 days before screening; use of a study-prohibited medication within 4 weeks of signing the informed consent form; use of study-prohibited agents, medications known to increase adverse events, or cytochrome P450 3A4 inhibitors during treatment. Patients were also excluded if they currently had an untreated psychiatric disease; unstable endocrine disease; uncontrolled hypothyroidism, hypertension, or cardiac arrhythmias; acute or subacute peripheral artery disease occlusion; congestive heart failure (New York Heart Association class III or IV); unstable angina, non–ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction, angioplasty, recent coronary bypass surgery, stroke, transient ischemic attack, deep vein thrombosis within the previous 3 months; poorly controlled type I or II diabetes; history of bleeding diathesis; active peptic ulcer or active liver disease (hepatitis B and/or C); active gallbladder disease within the previous 12 months; chronic or acute pancreatitis within the previous 6 months; cancer within the last 5 years (excluding basal cell carcinoma of the skin); or any health condition/laboratory abnormality that would be adversely affected by the procedures or medications in this study. Patients with the following laboratory values were also excluded: creatine phosphokinase (CPK) >3× upper limit of normal (ULN), alanine aminotransferase (ALT) >1.3× ULN, aspartate aminotransferase (AST) >1.3× ULN, calculated creatinine clearance <30 mL/min, glycosylated hemoglobin (HbA_{1c}) ≥9%, or uric acid levels ≥1.3× ULN.

Screening phase

The screening phase was a minimum of 4 weeks long and included three to four visits to the clinic. During this