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Comparison of the effect of simvastatin versus simvastatin/ezetimibe versus rosuvastatin on markers of inflammation and oxidative stress in subjects with hypercholesterolemia

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ABSTRACT

Objectives: Statins may exhibit anti-inflammatory and antioxidant effects. Whether different statins at equivalent doses or the combination of low-dose statin with ezetimibe have comparable anti-inflammatory and antioxidant effects is unknown. The aim of this study was to compare the effects of simvastatin, simvastatin/ezetimibe or rosuvastatin at equivalent low-density lipoprotein cholesterol lowering doses on inflammation and oxidative stress indices in subjects with hypercholesterolemia.
Methods: This was a pre-specified analysis of a prospective, randomized, open-label, blinded endpoint (PROBE) study. We enrolled one hundred and fifty three ($n = 153$) hypercholesterolemic subjects who were randomized to receive simvastatin 40 mg or simvastatin/ezetimibe 10/10 mg or rosuvastatin 10 mg daily. Plasma 8-Epi prostaglandin F2 alpha (8-epiPGF2a), oxidized LDL (oxLDL) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity and mass were measured at baseline and following 12 weeks of treatment.
Results: A significant reduction in plasma 8-isoprostane and oxLDL levels was observed in all treatment groups [by 10%, 8% and 6% ($p < 0.05$ compared with baseline) and 41%, 40% and 39% ($p < 0.001$ compared with baseline) in simvastatin, simvastatin/ezetimibe and rosuvastatin groups, respectively]. In all treatment groups a significant reduction in total plasma Lp-PLA_2 activity and mass was observed (by 36%, 31% and 38% and 36%, 32% and 32% for simvastatin, simvastatin/ezetimibe and rosuvastatin, respectively, $p < 0.001$ compared with baseline). No intergroup differences were observed.
Conclusions: Simvastatin 40 mg, simvastatin/ezetimibe 10/10 mg and rosuvastatin 10 mg significantly reduced 8-epiPGF2a, oxLDL and Lp-PLA_2 activity and mass to a similar extent.

1. Introduction

Oxidative stress and inflammation represent integral features of atherogenesis and vascular disease. The oxidative modification of low-density lipoprotein (LDL) particles in the subendothelium of vessels is one crucial step in atherogenesis. At the same time, a wide range of cytokines, growth factors and enzymes such as phospholipases A_2 are produced and secreted by activated macrophages within the inflamed atherosclerotic plaque. Oxidatively modified LDL particles are capable of activating immune responses and thus propagating the inflammatory cascade [1].

Statins are considered the cornerstone for cardiovascular risk reduction [2]. Current data substantiate that the overall benefits of statins may not be attributed entirely to their lipid-lowering properties, but also to cholesterol-independent or "pleiotropic" effects [3]. Pleiotropic effects include improvement in endothelial function, reduction in thrombogenic responses and oxidative stress and inflammation, as well as stabilization of the atherosclerotic plaque. These pleiotropic effects are mainly mediated by inhibition of isoprenoids, which serve as lipid attachments for intracellular signaling molecules [3].

Current approaches to reduce low-density lipoprotein cholesterol (LDL-C) in clinical practice include either a statin or the combination of statin plus ezetimibe. Ezetimibe results in substantial reduction in LDL-C levels when added to a statin [4,5]. However, it remains a matter of debate whether ezetimibe exert

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Abbreviations

8-epiPGF2a	8-epi prostaglandin F2 alpha
ANCOVA	analysis of covariance
Apo	apolipoprotein
BMI	body mass index
CK	creatinine kinase
CM–SC	gas chromatography–mass spectrometry
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
hsCRP	high-sensitivity C-reactive protein
IL	interleukin
LDL-C	low-density lipoprotein cholesterol
Lp-PLA$_2$	lipoprotein-associated phospholipase A$_2$
NCEP-ATP III	national cholesterol education program adult treatment panel III
oxLDL	oxidized LDL
PAF	platelet-activating factor
PROBE	prospective, randomized, open-label, blinded endpoint
SPSS	statistical package for the social sciences
TC	total cholesterol
TG	triglycerides
ULN	upper limit normal

pleiotropic effects or whether the combination of ezetimibe with a low-dose statin exert similar pleiotropic effects compared with high-dose statin monotherapy for the same degree of LDL-C lowering [6].

Whether different statins at equivalent LDL-C lowering doses or the combination of low-dose statin with ezetimibe have comparable anti-inflammatory and antioxidant effects is unknown.

We have previously described the effects of 3 hypolipidemic treatment regimens with similar LDL-C-lowering capacity, namely simvastatin 40 mg, simvastatin/ezetimibe 10/10 mg and rosuvastatin 10 mg, on lipids, high-sensitivity C-reactive protein (hsCRP) as well as glucose and uric acid metabolism in patients with primary hypercholesterolemia [7,8]. We now report on a pre-specified analysis regarding the effect of these treatments on plasma markers of oxidative stress (oxidized LDL [oxLDL], 8-Epi prostaglandin F2 alpha [8-epiPGF2a]) and inflammation [lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) activity and mass].

2. Materials and methods

2.1. Patient population

Study details have been previously described [7]. Patients were recruited from the Outpatient Lipid and Obesity Clinic of the University Hospital of Ioannina. A total of 153 patients were randomized. Patients with primary hypercholesterolemia with LDL-C levels above those recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) based on each patient risk factors following a 3-month period of lifestyle changes were included [2].

Exclusion criteria were known coronary artery disease, symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, renal disease (serum creatinine levels $>$ 1.6 mg/dL), hypothyroidism [thyroid stimulating hormone (TSH) $>$ 5 IU/mL], liver disease [alanine aminotransferase and/or aspartate aminotransferase levels $>$ 3-fold upper limit of normal (ULN) in 2 consecutive measurements], triglycerides (TG) $>$ 500 mg/dL, neoplasia as well as clinical and laboratory evidence of an inflammatory or infectious condition within 6 months preceding the study. Alcohol abusers ($>$2 drinks/day for men and $>$1 drink/day for women) were excluded. Patients with hypertension were included if they were on stable medication for at least 3 months and their blood pressure was adequately controlled (systolic blood pressure $<$ 140 mmHg and diastolic blood pressure $<$ 90 mmHg; no change in their treatment was allowed during the study). Patients taking anti-inflammatory drugs were excluded. Patients currently taking lipid-lowering drugs or having stopped them less than 12 weeks before study entry, as well as patients with a history of adverse reactions to statins or ezetimibe were excluded. Females receiving hormonal replacement therapy or oral contraceptives were also excluded. No female patient with polycystic ovary syndrome was included. Use of any plant stanol esters, drugs or supplements that are known to affect plasma cholesterol was not allowed. Patients taking immunosuppressants, corticosteroids, or potent CYP3A4 inhibitors were also excluded. All concomitant therapies were monitored in enrolled subjects, and no change in their treatment was made during study period.

2.2. Study protocol

This is a prespecified analysis of a prospective, randomized, open-label, blinded endpoint (PROBE) study. Recruitment took place from July 2009 through July 2010. Initially, 160 Caucasians patients were enrolled (Fig. 1). All participants received a 3-month dietary lead-in according to the NCEP ATP III guidelines. A dietician prescribed a low fat diet for each patient. All participants were advised to follow regular physical activity (walking, jogging, swimming). There were no differences in diet composition or advice provided between the study groups.

After a 3-month dietary intervention, 153 patients (56 male) continued to meet the inclusion criteria and were randomized to receive either simvastatin 40 mg (n = 55) or rosuvastatin 10 mg (n = 45) or the combination of simvastatin 10 mg with ezetimibe 10 mg (n = 53; as a single pill) for 12 weeks (Fig. 1). Randomization was performed by means of a computer-generated sequence of random numbers. Participants were instructed to take tablets once daily in the evening.

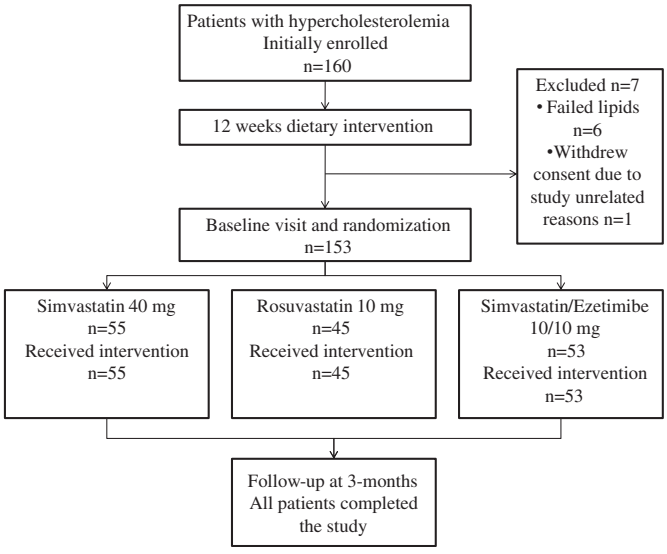

Fig. 1. Study participants' flow diagram.