International Journal of Cardiology 199 (2015) 126–131

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia

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ARTICLE INFO

Article history:
Received 3 June 2015
Accepted 6 July 2015
Available online 11 July 2015

Keywords:
Statins
Ezetimibe
Insulin resistance
Fat
Hypercholesterolemia hypertension

ABSTRACT

Background: Ezetimibe demonstrates decreasing visceral fat and improving insulin sensitivity (IS) in animals and humans. We first reported that simvastatin dose-dependently worsens insulin sensitivity. Whether ezetimibe may compensate untoward effects of simvastatin, depending on dosages of simvastatin has not been investigated in patients with hypercholesterolemia, compared with simvastatin alone.
Methods: This was a randomized, single-blind, placebo-controlled, parallel study. Fifty-one in each group were given placebo, ezetimibe 10 mg combined with simvastatin 10 mg (Vyto10), ezetimibe 10 mg combined with simvastatin 20 mg (Vyto20), or simvastatin 20 mg alone (Simva20) daily for 2 months.
Results: Placebo, Vyto10, Vyto20, and Simva20 improved flow-mediated dilation relative to baseline measurements. Placebo therapy did not significantly change insulin and IS and adiponectin levels and visceral fat area (VFA) and VFA/subcutaneous fat area (SFA) relative to baseline measurements. Vyto10 therapy significantly decreased CRP and insulin levels and increased adiponectin levels and IS, and reduced VFA, VFA/SFA, and blood pressure. Vyto20 therapy did not significantly change insulin levels and IS and adiponectin levels but significantly reduced CRP levels and VFA, VFA/SFA, and blood pressure. Simva20 therapy significantly decreased adiponectin levels and IS but did not significantly change VFA, VFA/SFA, and blood pressure. Of note, these different effects of each therapy were significant by ANOVA.
Conclusions: Vyto10, Vyto20, and Simva20 showed significant reduction of LDL cholesterol levels and improvement of flow-mediated dilation in patients with hypercholesterolemia. However, Vyto10, Vyto20, and Simva20 showed significantly differential metabolic effects, depending on dosages of simvastatin.

1. Introduction

Statin therapy has reduced coronary heart disease events significantly by reducing low-density lipoprotein (LDL) cholesterol levels. Nonetheless, many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol [1]. Coronary heart disease is characterized by endothelial dysfunction and frequently clusters with disorders of metabolic homeostasis characterized by insulin resistance. These co-morbidities may be explained, in part, by mutual relationships between endothelial dysfunction and insulin resistance [2–4].

With regard to beneficial effects of statins on endothelial dysfunction, all statins improve nitric oxide bioavailability resulting in improved flow-mediated dilator response to hyperemia (FMD) [5,6]. On the other hand, statins dose-dependently worsen insulin sensitivity [7]. Indeed, we reported that simvastatin and atorvastatin dose-dependently worsen insulin sensitivity by reducing plasma levels of adiponectin in humans [8,9].

Experimental studies demonstrated that ezetimibe improves liver steatosis and insulin sensitivity in rat model of metabolic syndrome [10] and diet-induced obesity and diabetes in mice [11]. Addition of ezetimibe to a weight loss diet in obese subjects significantly improved hepatic steatosis [12]. Ezetimibe reduced visceral fat with beneficial effects on adiponectin and insulin resistance in patients with metabolic syndrome [13].

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http://dx.doi.org/10.1016/j.ijcard.2015.07.016
0167-5273/

We reported that losartan compensated untoward effects of simvastatin in patients [14]. When combined with simvastatin, ezetimibe may compensate untoward effects of simvastatin, but no studies reported whether its effect depends on dosages of simvastatin. Therefore, we investigated the effects of different dosages of simvastatin combined with ezetimibe on FMD, insulin sensitivity, visceral fat, and blood pressure in patients with hypercholesterolemia, compared with simvastatin alone.

2. Methods

2.1. Study population and design

We used a randomized, single-blind, placebo-controlled, parallel study design. Age, gender, and body mass index were matched among all subjects. We recruited patients from a primary care setting in Cardiology Clinic, Gil Medical Center, Gachon University. Before and during the study period a dietitian educated patients to maintain a low fat diet. Patients with hypercholesterolemia (LDL cholesterol levels ≥130 mg/dl) participated in this study. We excluded patients with overt liver disease, chronic renal failure, hypothyroidism, myopathy, uncontrolled diabetes, severe hypertension, stroke, acute coronary events, coronary revascularization within the preceding 3 months, or alcohol abuse. No patient had taken any lipid-lowering agent, hormone replacement therapy, or antioxidant vitamin supplements during the 2 months preceding our study. Each of the fifty-one in each group was given placebo, ezetimibe 10 mg combined with simvastatin 10 mg (Vyto10), ezetimibe 10 mg combined with simvastatin 20 mg (Vyto20), or simvastatin 20 mg alone (Simva20) once daily during a 2 month treatment period. Allocation concealment was achieved by using envelopes with the collaboration of a statistician. A research nurse counted pills at the end of treatment to monitor compliance. The patients were seen at least every one month during the study. To minimize side effects, we measured serum aspartate aminotransferase, alanine aminotransferase, creatine kinase, blood urea nitrogen and creatinine before and after therapy. One patient on Vyto20 withdrew from the study because he moved to other places and dropped out of the study. Thus, 51 patients on placebo, 51 patients on Vyto10, 50 patients on Vyto20, and 51 patients on Simva20 finished the study. Clinical characteristics of these patients are summarized in Table 1. No additional medications including aspirin or non-steroidal anti-inflammatory drugs were allowed during the study period to avoid confounding effects of other drugs. Calcium channel or beta adrenergic blockers were withheld for ≥48 h before the study. This study was approved by the Gil Hospital Institutional Review Board and all participants gave written, informed consent.

2.2. Laboratory assays and vascular studies

Blood samples for laboratory assays were obtained at approximately 8:00 a.m. following overnight fasting before and at the end of 2-month treatment period. These samples were immediately coded so that investigators performing laboratory assays were blinded to subject identity or study sequence.

Assays for lipids, glucose, and plasma adiponectin were performed in duplicate by ELISA (R & D Systems, Inc., Minneapolis, Minnesota), assays for high sensitivity C-reactive protein (CRP) levels by latex agglutination (CRP-Latex(II)®, Denka-Seiken, Tokyo, Japan) and assays for plasma insulin levels by immunoradiometric assay (INSULIN-RIABEAD® II, SRL, Inc., Tokyo, Japan) and assays for ambient glycemia, glycated hemoglobin ($HbA1_C$) by high performance liquid chromatography assay (VARIANT II TURBO®, BIO-RAD, Inc., Hercules, California) as previously described [8,9,15–18]. The interassay and intraassay coefficients of variation were <6%. Quantitative Insulin-Sensitivity Check Index (QUICKI), a surrogate index of insulin sensitivity based on fasting glucose and insulin levels, was calculated as follows (insulin is expressed in μU/ml and glucose in mg/dl): $QUICKI = 1 / [\log(\text{insulin}) + \log(\text{glucose})]$ [19,20]. Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine (ATL Philips, Bothell, WA, USA) equipped with a 10 MHz linear-array transducer, based on a previously published technique [8,15–18]. The intra-abdominal visceral fat area (VFA) and the subcutaneous fat area (SFA) were obtained by the computed tomography (CT) scan (SOMATOM Sensation 64; Siemens Healthcare, Forchheim, Germany). 10 mm CT slices were obtained at the umbilical level and the average value of pixels within the range of −200 to −20 Hounsfield units was used for measurement of abdominal fat areas [21]. The images were analyzed with a commercial software program (syngo Volume; Siemens Healthcare, Forchheim, Germany). Measurements were performed by two independent investigators (Oh PC, Kim EY) blinded to the subject's identity and medication status. Measurements were made in 10 studies selected at random. Pearson's correlation coefficients of intra-observer variability for repeated measurement of SFA and VFA were 0.987 and 0.982, respectively. Pearson's correlation coefficients of inter-observer variability for repeated measurement of SFA and VFA were 0.978 and 0.970, respectively. It is reasonable to establish the cut-off point of VFA at 100 cm^2 as indicative of the risk of obesity-related disorders [22].

Table 1
Baseline characteristics of the study population.

	Placebo (n = 51)	Vyto10 (n = 51)	Vyto20 (n = 50)	Simva20 (n = 51)
Risk factors, n (%)				
Current smoking	4 (8)	3 (6)	3 (6)	2 (4)
Stable angina	3 (6)	3 (6)	1 (2)	2 (4)
Diabetes	2 (4)	2 (4)	2 (4)	1 (2)
Hypertension	10 (20)	10 (20)	8 (16)	9 (18)
Medications, n (%)				
β-Adrenergic blockers	7 (14)	6 (12)	6 (12)	8 (16)
Calcium channel blockers	30 (59)	28 (55)	28 (56)	32 (63)

2.3. Statistical analysis

Data are expressed as mean ± SD or median (range: 25%–75%). After testing data for normality, we used Student's paired *t* or Wilcoxon Signed Rank test to compare values between baseline and treatment at 2 months, as reported in Table 2. We used one way analysis of variance (ANOVA) or Kruskal–Wallis ANOVA on Ranks to compare baseline or treatment effects among the treatment groups. Post-hoc comparisons between different treatment pairs were made using the Student–Newman–Keuls multiple comparison procedures or Dunn's method. Pearson or Spearman correlation coefficient analysis was used to assess associations between measured parameters, as reported in Table 2. We calculated that 40 subjects would provide 80% power for detecting an absolute increase of 1.7% or greater in FMD between baseline and Simva20, with $\alpha = 0.05$ based on our previous studies [8]. The comparison of endothelium-dependent dilation was prospectively designated as the primary end-point of the study. All other comparisons were considered secondary. A value of $P < 0.05$ was considered to represent statistical significance.

3. Results

There were no significant differences between groups for any of the baseline measurements (Table 2).

3.1. Effects on vasomotor function

Each therapy significantly improved FMD relative to baseline measurements. These beneficial effects of Vyto10, Vyto20, and Simva20 were also significant when compared with placebo (all $P < 0.001$ by ANOVA; Table 2). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies.

3.2. Effects of therapies on blood pressure

Vyto10 and Vyto20 therapies significantly reduced systolic and diastolic blood pressure after 2 month administration when compared with baseline. Of note, there were significant differences among each therapy for systolic blood pressure ($P = 0.044$ by ANOVA). These reductions with Vyto20 were significantly greater than those observed with Simva20 alone ($P < 0.05$ by post-hoc comparison). However, there were no significant differences among each therapy for diastolic blood pressure ($P = 0.138$ by ANOVA, Fig. 1, Table 2).

3.3. Effects on lipids

Each therapy significantly reduced total cholesterol, LDL cholesterol, apolipoprotein B, and non-high-density lipoprotein (non-HDL) cholesterol levels from baseline (all $P < 0.05$ by paired *t*-test) after 2 month administration. These beneficial effects of Vyto10, Vyto20, and Simva20 were also significant when compared with placebo treatment (all $P < 0.001$ by ANOVA; Fig. 2, Table 2). Vyto20 significantly reduced total cholesterol, LDL cholesterol, non-HDL cholesterol levels when compared with Vyto10 or Simva20 ($P < 0.05$ by post-hoc comparison) after 2 month administration. Vyto10 significantly reduced total cholesterol, LDL cholesterol, non-HDL cholesterol levels when compared with Simva20 ($P < 0.05$ by post-hoc comparison) after 2 month administration. Of note, when compared with Vyto10 and Vyto20, Simva20 significantly increased HDL cholesterol levels ($P = 0.001$ by ANOVA).