Atherosclerosis 226 (2013) 161–164

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

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

Effects of pitavastatin and atorvastatin on lipoprotein oxidation biomarkers in patients with dyslipidemia

Hiroshi Yoshida [a,b,*], Toru Shoda [a], Hidekatsu Yanai [c], Katsunori Ikewaki [d], Hideaki Kurata [e], Kumie Ito [b], Nobuyuki Furutani [b], Norio Tada [b], Joseph L. Witztum [f], Sotirios Tsimikas [f]

[a] Department of Laboratory Medicine, Jikei University Kashiwa Hospital, Chiba, Japan
[b] Department of General Medicine, Jikei University Kashiwa Hospital, Chiba, Japan
[c] Department of Internal Medicine, Konodai National Medical Center, Ichikawa, Chiba, Japan
[d] Department of Anti-aging Medicine, National Defense Medical College, Tokorozawa, Saitama, Japan
[e] Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University Katsushika Medical Center, Tokyo, Japan
[f] Department of Medicine, University of California San Diego, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 29 January 2012
Received in revised form
29 October 2012
Accepted 29 October 2012
Available online 8 November 2012

Keywords:
Statin
MDA-LDL
OxPL/apoB
Lp-PLA_2
Biomarkers
Cardiovascular disease

ABSTRACT

Objective: The effects of potent statins on oxidized lipoprotein biomarkers are not well defined.
Methods and results: The VISION (Value of oxIdant lipid lowering effect by Statin InterventiON in hypercholesterolemia) Trial randomized patients with hypercholesterolemia to 12-week administration of pitavastatin 2 mg/day ($n = 21$) or atorvastatin 10 mg/day ($n = 21$) and a variety of lipoprotein oxidative biomarkers were measured. Between-group analysis did not reveal any differences except in the ratio of malondialdehyde (MDA)-LDL over apolipoprotein B-100 (MDA-LDL/apoB) in pitavastatin vs. atorvastatin group (−13% vs. −0.7%, $p = 0.04$). Within-group changes from baseline to 12-week revealed significant increases in OxPL/apoB and reductions in small-dense LDL, MDA-LDL, and lipoprotein-associated phospholipase A_2 measured on circulating apoB particles (Lp-PLA_2/apoB) in both groups and significant reductions in OxPL/apoAI in the atorvastatin group.
Conclusions: The VISION study describes the first comparison on lipoprotein oxidation biomarkers between pitavastatin and atorvastatin and suggests diverse effects on lipoprotein oxidation markers in patients with hypercholesterolemia.

1. Introduction

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are effective at decreasing serum levels of low-density lipoprotein cholesterol (LDL-C) and reducing cardiovascular disease (CVD) risk [1]. Their effects are mainly attributed to LDL-C lowering, but pleiotropic effects such as reduction of oxidative stress may play an important role in the initiation and progression of atherosclerotic disease [2]. Oxidized LDL (OxLDL) is generated from accumulation of LDL particles in the vessel wall and is postulated to be a significant etiologic agent in CVD. OxLDL is not one homogenous entity but contains many different types of chemical and immunogenic modifications of lipids and apolipoprotein B-100 (apoB) [3,4]. Assays that measure oxidized phospholipids (OxPL) on apoB (OxPL/apoB) and malondialdehyde (MDA)-LDL have been developed as a cardiovascular biomarkers [5–7]. These novel assays may provide additional insights into the benefits of statin therapy.

The LDL oxidation hypothesis is supported by evidence that OxLDL is present in vivo, leads to foam cell formation, and promotes progression of atherosclerotic lesions [3,6,7]. Circulating OxLDL is a well-known risk marker of CVD [3–8]. The presence of oxidation-specific epitopes in human atherosclerotic aortic lesions was reported previously [3,6–9].

Recently, Japanese investigators demonstrated that the administration of pitavastatin 4 mg/day and atorvastatin 20 mg/day in JAPAN-ACS study [10] resulted in equivalent reductions in coronary plaque volume in patients with acute coronary syndrome. This study also showed a similar decrease in circulating MDA-LDL in the two statin groups, suggesting that some of the benefits may be through reductions in oxidized lipoproteins.

In the current study, we randomized patients to pitavastatin 2 mg/day and atorvastatin 10 mg/day and evaluated their effects on a variety of biomarkers of oxidized lipoproteins.

* Corresponding author. Department of Laboratory Medicine, Jikei University Kashiwa Hospital, 163-1 Kashiwashita, Kashiwa, Chiba 277-8567, Japan. Tel.: +81 4 7164 1111x2270; fax: +81 4 7164 1126.
E-mail address: hyoshida@jikei.ac.jp (H. Yoshida).

0021-9150/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2012.10.069

2. Methods

2.1. Study subjects

The VISION (Value of oxIdant lipid lowering effect by Statin InterventiON in hypercholesterolemia) study complies with the Declaration of Helsinki, was approved by the Ethics Committee of Jikei University School of Medicine and registered at UMIN Clinical Trials Registry (UMIN-000001783). Forty-seven patients (20 men and 27 postmenopausal women) with hyperlipidemia, aged 45–75 years, were recruited. Exclusion criteria included subjects with age <20 years, premenopausal females, diabetes, CVD, liver dysfunction, renal dysfunction, endocrine disease, or administration of agents affecting lipid metabolism and lipid oxidation. After the informed consent, 3 from the pitavastatin group and 2 from the atorvastatin group dropped out of the study. Therefore, 42 subjects were randomized to the 2 treatment groups and completed the study.

2.2. Study design and laboratory measurements

Patients were randomized into two 12-week treatment groups with pitavastatin 2 mg/day ($n = 21$) or atorvastatin 10 mg/day ($n = 21$), and were asked to maintain their habitual diet and lifestyle throughout the study. After 12-h overnight fasting, venous blood was collected in EDTA-2Na tubes, and underwent anthropometric and blood pressure measurements at baseline and end of the study. The study was designed as a pilot study and the primary comparison was the differences in oxidative biomarkers between the pitavastatin and atorvastatin groups. Secondary comparisons were within-groups differences in each group from baseline to 12 weeks. The overall goal was to derive hypothesis-generating data to design a larger trial with appropriate statistical power, as many of these biomarkers have not been previously measured in statin trials and none were previously measured with pitavastatin.

Fasting plasma glucose, hemoglobin (Hb)A1c, insulin, serum total cholesterol (TC), triglyceride (TG), apoAI, apoB, and lipoprotein(a) [Lp(a)] were determined by standard methods, and LDL- and HDL-C were measured by homogenous methods (Sekisui Medical Co., Tokyo, Japan). Small dense (sd)-LDL-cholesterol was measured by a direct homogenous assay in the supernatant that remained after heparin-magnesium precipitation of lipoproteins with density <1.044 g/ml [11]. MDA-LDL was measured by an enzyme-linked immunosorbent assay method (Sekisui Medical Co.) with mouse monoclonal antibody ML25 against MDA residues [4,7]. The intra-assay and inter-assay CVs were 4.3% and 8.5% for MDA-LDL. The ratio of MDA-LDL/apoB was also determined by dividing the MDA-LDL data with plasma apoB (MDA-LDL/apoB). The following assays were measured at the University of California San Diego (UCSD): oxidized phospholipids on apolipoprotein B-100 (OxPL/apoB) as well described [5], OxPL/apo(a), OxPL/apoAI, and lipoprotein-associated phospholipase A_2 measured directly on apoB(Lp-PLA_2/apoB), apo(a) (Lp-PLA_2/apo(a)) and apoAI (Lp-PLA_2/apoAI) particles captured on microtiter well plates as recently described [12]. The intra-assay and inter-assay CVs for the OxPL/apoB is 5–10% as described [5]. The other UCSD assays are relatively new and there is not enough clinical data to derive accurate CVs yet. In the current experiments, the CVs were 5–15%. A detailed review of the various oxidation-specific epitopes is given in Tsimikas and Miller [8]. Plasma vitamin E concentrations were measured by the conventional HPLC method [13].

2.3. Statistical analysis

Values are given as mean ± standard deviation. Significance in differences between and within statin groups before and after administration was assessed by paired *t*-test or unpaired *t*-test as appropriate. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and changes in standard lipid parameters

There were no significant baseline characteristic differences between groups (Table 1).

There were no significant differences in baseline values of TC, TG, HDL-C, LDL-C, non-HDL-C, apo A1, and apoB between groups (Table 2). Pitavastatin and atorvastatin significantly decreased LDL-C, apoB, non-HDL-C, and TG, and there were no significant differences in the mean % change between statins. Pitavastatin significantly increased HDL-C and apoA-1 ($p = 0.01$), whereas atorvastatin did not change those, but the difference in % changes were not significant between groups ($p = 0.08$).

3.2. Parameters of oxidized lipoproteins, sd-LDL, Lp(a), and vitamin E

There were no significant baseline differences in oxidized lipoproteins, sd-LDL, Lp(a), and vitamin E between groups (Table 2). Vitamin E levels were decreased similarly by pitavastatin and atorvastatin, presumably reflecting the decrease in lipoproteins which are carriers of vitamin E.

Between-group analysis did not reveal any differences between groups except for the ratio of malondialdehyde (MDA)-LDL over apolipoprotein B-100 (MDA-LDL/apoB) in pitavastatin vs. atorvastatin group (−13% vs. −0.7%, $p = 0.04$). Within-group changes from baseline to 12-week revealed significant increases in OxPL/apoB and reductions in small-dense LDL, MDA-LDL, and lipoprotein-associated phospholipase A_2 measured on circulating apoB particles (Lp-PLA_2/apoB) in both groups and significant reductions in OxPL/apoAI in the atorvastatin group (Table 2).

4. Discussion

The present study performed the first comparison between pitavastatin and atorvastatin on a variety of established and emerging lipoprotein oxidation biomarkers. Pitavastatin had a greater reduction in MDA-LDL/apoB but otherwise no differences were noted in the other biomarkers compared to atorvastatin.

Table 1
Baseline characteristics of study subjects.

	Pitavastatin ($n = 21$)	Atorvastatin ($n = 21$)	Difference (*p*.value)
Age (year)	59.7 (8.7)	61.5 (7.9)	0.48
Male/Female (*n*/*n*)	7/14	9/12	0.53
BMI (kg/m^2)	24.6 (2.9)	23.8 (3.9)	0.43
Waist circumference (cm)	87.7 (9.6)	83.3 (10.2)	0.16
Blood pressures (mmHg)			
Systolic	124 (11)	125 (10)	0.67
Diastolic	77 (6)	76 (7)	0.53
Hypertension (n)	9	7	0.32
HbA1c (%)	5.3 (0.4)	5.2 (0.3)	0.25
HOMA-R	1.65 (1.22)	1.28 (0.62)	0.22

HbA1c levels are expressed according to the procedures outlined by the Laboratory Test Committee of the Japan Diabetes Society.
HOMA-R was calculated by the formula [fasting plasma glucose (mg/dl) times fasting serum insulin (μU/ml) over 405].
BMI and HOMA-R mean body mass index and homeostasis model assessment ratio, respectively.
Significance differences between statin groups and within stain groups before and after statin administration was assessed by unpaired *t*-test analysis.