The effect of combining rosuvastatin with sartans of different peroxisome proliferator receptor-γ activating capacity on plasma 8-isoprostane prostaglandin F_{2a} levels

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Abstract

Introduction: Oxidative stress is associated with the development and progression of cardiovascular disease. Plasma 8-isoprostane prostaglandin F_{2a} (8-iso-PGF_{2a}) levels are a reliable marker of oxidative stress.
Material and methods: Patients (n = 151) with hypertension, dyslipidemia and impaired fasting glucose were randomly allocated to rosuvastatin (10 mg/day) plus telmisartan 80 mg/day (RT group, n = 52) or irbesartan 300 mg/day (RI group, n = 48) or olmesartan 20 mg/day (RO group, n = 51). After 6 months of treatment, changes in plasma 8-iso-PGF_{2a} levels were blindly evaluated.
Results: A decrease of 8-iso-PGF_{2a} levels vs baseline was observed only in the RT group (–8.6%; p = 0.02). A trend for decrease vs. baseline was observed in the RI (–5.7%; p = 0.40) and RO (–3.7%; p = 0.60) groups. Changes of 8-iso-PGF_{2a} levels between groups were not significantly different (p = 0.70).
Conclusions: The combination of rosuvastatin with sartans of different peroxisome proliferator receptor-γ activating capacity was associated with a decrease in levels of plasma 8-iso-PGF_{2a}. This decrease reached significance only in the telmisartan group.

Key words: rosuvastatin, telmisartan, olmesartan, irbesartan, oxidative stress.

Introduction

Hypercholesterolemia and high blood pressure are at the cornerstone of cardiovascular disease (CVD) development and progression and often coexist. In the context of comprehensive management [1, 2], the combination of a statin with an angiotensin receptor blocker (ARB) is common. Oxidative stress plays an important role in the pathogenesis and development of CVD [3, 4]. The isoprostanes are a family of eicosanoids of non-enzymatic origin produced by the random oxidation of tissue phospholipids by oxygen radicals. Levels of 8-isoprostane prostaglandin F_{2a} (8-iso-PGF_{2a}) have been established as a reliable marker of oxidative stress [5-7] and coronary heart disease [8]. Statins have a favorable or neutral effect on oxidative stress markers [9, 10]. The peroxisome proliferator receptor γ (PPAR-γ) modifies the expression of numerous metabolic related genes and could therefore play a role in oxidative stress.

Thiazolidinediones have been shown to hold antioxidative pleiotropic effects beyond glucose lowering [11, 12]. Some ARBs, mainly telmisartan and to a lesser degree irbesartan, have the ability to partially activate PPAR-γ [13]. This trait of some ARBs may differentiate their effect on oxidative stress.

The present study evaluated the effects of combining a statin with ARBs of different capacity to activate PPAR-γ on plasma 8-iso-PGF_{2a} levels.

Material and methods

Subjects

This is a pre-specified analysis of a previously reported study [14]. In brief, patients attending the Outpatient Lipid Clinic of the University Hospital of Ioannina, Greece were recruited. Eligible patients were those with impaired fasting plasma glucose, mixed dyslipidemia and stage 1 hypertension. Patients were excluded if they had any of the following: (1) history of diabetes, (2) history of CVD, (3) elevated triglycerides (TG) (> 400 mg/ dl; 4.52 mmol/l), (4) kidney disease, (5) hypothyroidism, (6) liver dysfunction, (7) receiving lipid-lowering or antihypertensive treatment in the last 3 months prior to recruitment and (8) females who did not take sufficient contraceptive measures.

All participants gave written informed consent and the study protocol was approved by our institutional ethics committee.

Study design

All patients (n = 159) received a 12-week dietary intervention in accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines and the Dietary Approaches to Stop Hypertension (DASH) diet [15]. Patients (n = 151) who continued to meet the inclusion criteria after the dietary intervention period were randomly allocated to open-label: i) rosuvastatin (10 mg/day) plus a sartan with partial PPAR-γ activating capacity (telmisartan 80 mg/day; n = 52; RT group), ii) rosuvastatin (10 mg/day) plus a sartan with weak partial PPAR-γ activating capacity (irbesartan 300 mg/day; n = 48; RI group) or iii) rosuvastatin (10 mg/day) plus a sartan without PPAR-γ activating capacity (olmesartan 20 mg/day; n = 51; RO group).

Selected doses of studied drugs are the usual starting doses in clinical practice in our country. Moreover, selected sartan doses are equivalent in terms of blood-pressure lowering.

Compliance with study medication was assessed at week 24 by counting taken tablets; patients were considered compliant if they took 80-100% of the prescribed number of tablets.

Biochemical parameters

All laboratory determinations were carried out after an overnight fast as previously described [14] at baseline (which was after the 12-week dietary intervention) and at 6 months after initiation of treatment. Laboratory determinations were performed blindly with regard to treatment allocation. Plasma levels of 8-iso-PGF_{2a} were determined by means of a competitive ELISA using a commercially available kit (Cayman Chemicals, Ann Arbor, MI) [16].

Statistical analysis

Values are given as mean ± standard deviation (SD) and median (range) for parametric and non-parametric data, respectively. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test and logarithmic transformations were accordingly performed for non-parametric variables. The paired-sample t-test was used for assessing the effect of treatment in each group. Analysis of covariance (ANCOVA), adjusted for baseline values, was used for comparisons between treatment groups. Significance was defined as $p < 0.05$. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 (SPSS Inc, Chicago, IL). In a post hoc calculation, given the effect size, the alpha level, and the sample size, we calculate that the achieved power of this pre-specified analysis to find a significant difference for the 8-iso-PGF_{2a} was above 95%.

Results

A total of 159 patients (76 males, mean age 60 years) were enrolled. Of them, 151 (73 males, mean age 60 years) continued to meet the inclusion criteria after the dietary intervention period and were randomized to the 3 groups. No patient dropped out and compliance was > 80% in all patients. No significant differences regarding baseline data were found across groups (Table I). The effects of all combinations on metabolic parameters have been previously described [14]. In brief, after the study end no differentiation in anthropometric variables and blood pressure was observed between groups. In addition, lipid profile was similarly altered in all groups (Table II). However, the homeostasis model assessment insulin resistance (HOMA-IR) decreased only in the RT group while an increase was observed in the other 2 regimens (Table II).

Plasma levels of 8-iso-PGF_{2a} vs. baseline decreased significantly only in the RT group (–8.6%; p = 0.02) (Table II). A non-significant trend for decrease vs. baseline was observed in the RI (–5.7%; p = 0.40) and RO (–3.7%; p = 0.60) groups (Table II). The changes of plasma 8-iso-PGF_{2a} levels between groups were not significantly different (p = 0.70).

Table I. Baseline demographic characteristics of study participants*

Parameter	RT group (n = 52)	RI group (n = 48)	RO group (n = 51)
N (females/males)	25/27	26/22	27/24
Age [years]	60 ±10	60 ±10	58 ±12
Smokers [%]	22	27	23
Body mass index [kg/m^2]	29 ±4	29 ±5	28 ±4
Waist circumference [cm]	101 ±9	101 ±11	100 ±8
Systolic blood pressure [mm Hg]	153 ±14	152 ±11	151 ±11
Diastolic blood pressure [mm Hg]	91 ±10	90 ±9	93 ±8

*RT – rosuvastatin + telmisartan, RI – rosuvastatin + irbesartan, RO – rosuvastatin + olmesartan, NS – not significant. *Values are expressed as mean ± SD; p = NS for all comparisons*

Table II. Serum metabolic parameters at baseline and after 6 months of treatment*

Variables	Baseline*	6 months*	Change [%]
Total cholesterol [mg/dl (mmol/l)]			
RT Group	271 ±29 (7.0 ±0.8)	177 ±28 (4.6 ±0.7)	–35‡
RI Group	269 ±23 (7.0 ±0.6)	170 ±30 (4.4 ±0.8)	–37‡
RO Group	274 ±27 (7.0 ±0.7)	175 ±32 (4.5 ±0.8)	–36‡
Triglycerides [mg/dl (mmol/l)]			
RT Group	180 (152-290) [2.0 (1.7-3.3)]	135 (81-270) [1.5 (0.9-3.1)]	–25‡
RI Group	173 (151-276) [3.3 (1.7-3.1)]	125 (77-252) [1.4 (0.9-2.9)]	–28‡
RO Group	187 (153-289) [2.1 (1.7-3.3)]	147 (76-210) [0.9 (1.7-2.4)]	–23‡
HDL-C [mg/dl (mmol/l)]			
RT Group	55 ±7 (1.4 ±0.2)	56 ±7 (1.4 ±0.2)	+1
RI Group	58 ±11 (1.5 ±0.3)	59 ±15 (1.5 ±0.4)	+1
RO Group	53 ±9 (1.4 ±0.2)	54 ±10 (1.3 ±0.3)	+2
LDL-C [mg/dl (mmol/l)]			
RT Group	182 ±23 (4.7 ±0.6)	105 ±28 (2.7 ±0.7)	–42‡
RI Group	176 ±23 (4.6 ±0.6)	99 ±22 (2.6 ±0.6)	–44‡
RO Group	183 ±22 (4.7 ±0.6)	99 ±31 (2.6 ±0.8)	–46‡
Fasting plasma glucose [mg/dl (mmol/l)]			
RT Group	112 ±10 (6.2 ±0.6)	113 ±9 (6.3 ±0.5)	+1.1
RI Group	110 ±10 (6.1 ±0.6)	112 ±7 (6.2 ±0.4)	+1.8
RO Group	114 ±11 (6.3 ±0.6)	114 ±8 (6.3 ±0.4)	0.0
HOMA-IR			
RT Group	2.6 (0.6-6.6)	1.8 (0.5-5.1)	–29†,¶,§
RI Group	2.5 (0.5-6.2)	2.9 (0.5-8.1)	+16†
RO Group	2.4 (0.5-7.9)	2.7 (0.5-5.2)	+14†
8-iso-PGF$_{2a}$ [pg/ml]			
RT Group	57.6 (26.0-91.0)	52.7 (25.1-88.6)	–8.6†
RI Group	51.8 (25.3-88.2)	48.9 (26.0-87.8)	–5.7
RO Group	54.3 (21.7-96.6)	52.3 (21.9-102.5)	–3.7

*RT – rosuvastatin + telmisartan, RI – rosuvastatin + irbesartan, RO – rosuvastatin + olmesartan, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, HOMA-IR – homeostasis model assessment insulin resistance, 8-iso-PGF$_{2a}$ – isoprostane 8-iso-prostaglandin F$_{2a}$. *Values are expressed as mean ± SD (except for triglycerides, HOMA-IR and 8-iso-PGF$_{2a}$, which are expressed as median (range)). †$p < 0.05$ vs. baseline, ‡$p < 0.001$ vs. baseline, ¶$p < 0.01$ vs. RI group, §$p < 0.05$ vs. RO group*

Discussion

The combination of rosuvastatin with sartans of different PPAR-γ activating capacity was associated with a decrease in levels of plasma 8-iso-PGF_{2a}. However, this decrease reached significance only in the telmisartan group.

Statins have been shown to have either a beneficial or neutral effect on oxidative stress markers. Fluvastatin was shown to possess antioxidant properties [9], rosuvastatin was associated with only a trend for decreasing oxidative stress [10], while atorvastatin showed a neutral effect on oxidative status [17]. The activation of the renin-angiotensin system (RAS) has been shown to promote oxidative stress [18, 19]. As a result, ARBs may have beneficial effects on oxidative stress. Indeed, irbesartan [20] and olmesartan [21] have been associated with a decrease in oxidative stress markers, while eprosartan was not associated with any changes of 8-iso-PGF_{2a} plasma levels [22]. Telmisartan was shown to decrease markers of oxidative stress vs. valsartan in type 2 diabetic patients with nephropathy [23].

Thiazolidinediones (TZDs), by activating PPAR-γ, increase insulin sensitivity. Thiazolidinediones have been shown to hold antioxidative effects beyond glucose lowering [11, 12]. Telmisartan, which partially activates PPAR-γ, may also possess additional antioxidative properties. The recent Effects of Simvastatin and Rosiglitazone Combination in patients with the metabolic syndrome (SIROCO) study showed that the combination of a statin (simvastatin) together with a PPAR-γ agonist (rosiglitazone) decreased markers of oxidative stress [24]. By combining a commonly used statin (rosuvastatin) with telmisartan, which partially activates PPAR-γ, an improvement of oxidative stress markers may be expected.

Indeed, a significant decrease in 8-iso-PGF_{2a} was seen only in the rosuvastatin/telmisartan group in this study. Although all ARBs may have to some degree antioxidative effects, telmisartan may possess additional such effects since it can activate the PPAR-γ receptors. On the other hand, this decrease was not significantly different when compared with the changes of 8-iso-PGF_{2a} in the other 2 groups. This finding puts into question whether telmisartan is indeed different compared with the other 2 sartans. It should be noted that the baseline values of 8-iso-PGF_{2a} were not particularly increased. Indeed, baseline levels of 8-iso-PGF_{2a} were very close to the normal levels of 8-iso-PGF_{2a}, which our group has measured using the same method in a previous study [7]. As a result, the potential of a drug treatment to further decrease the already near normal levels of 8-iso-PGF_{2a} is diminished.

A limitation of our study was that no other markers of oxidative stress were determined. Another limitation was the small number of participants. Moreover, a control group receiving rosuvastatin as monotherapy was not included since it was considered unethical to further delay antihypertensive treatment in these high-risk patients. Additional limitations include the open-label design, the relatively short period of follow-up as well as the fact that no oral glucose tolerance test was performed in patients with impaired fasting glucose to identify diabetic patients.

In conclusion, the combination of rosuvastatin with sartans of different PPAR-γ activating capacity was associated with a decrease in levels of plasma 8-iso-PGF_{2a}. This decrease reached significance only in the telmisartan group.

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