Differential Effect of *Telmisartan* and *Amlodipine* on Monocyte Chemoattractant Protein-1 and Peroxisome Proliferator-Activated Receptor-Gamma Gene Expression in Peripheral Monocytes in Patients With Essential Hypertension

Maria E. Marketou, MD[a], Joanna E. Kontaraki, PhD[a], Nikolaos A. Tsakountakis, MD[b], Evangelos A. Zacharis, MD[b], George E. Kochiadakis, MD[a], Dimitris A. Arfanakis, MD[a], Frangiskos Parthenakis, MD[a], Gregory Chlouverakis, PhD[c], and Panos E. Vardas, MD, PhD[a,*]

Monocyte chemoattractant protein-1 (MCP-1) and peroxisome proliferator-activated receptor-γ (PPAR-γ) play a significant role in monocyte activation, vascular inflammation, and atherogenesis. Angiotensin receptor blockers and calcium channel blockers are antihypertensive drugs with established efficacy and a favorable safety profile. We investigated the effect of telmisartan—an angiotensin receptor blocker with PPAR-γ agonist activity—and amlodipine on the activation state of peripheral blood monocytes with respect to MCP-1 and PPAR-γ gene expression in hypertensives. We recruited 31 previously untreated patients with essential hypertension who were randomly assigned to receive treatment with telmisartan (n = 16) or amlodipine (n = 15). Blood samples were taken before and 3 months after therapy initiation. Mononuclear cells were isolated and mRNAs of MCP-1 and PPAR-γ were estimated by real-time quantitative reverse transcription–polymerase chain reaction each time. The 2 treatments decreased all blood pressure components significantly ($p < 0.001$). In contrast, in the amlodipine group, MCP-1 gene expression was significantly downregulated after treatment with telmisartan (from 21.4 ± 20.5 to 8.1 ± 6.5, $p = 0.009$), whereas the amlodipine group did not show any significant change (12.5 ± 8.5 vs 17.6 ± 16.4, p = NS). In addition, PPAR-γ mRNA levels showed a significant increase in telmisartan-treated patients (from 20 ± 18.5 to 42.6 ± 36, $p = 0.006$) and no significant alterations in the amlodipine group (from 29.6 ± 42.5 to 24.2 ± 27.7, p = NS). In conclusion, treatment with telmisartan results in a significant attenuation of MCP-1 gene expression and an increase of PPAR-γ gene expression in peripheral monocytes in patients with essential hypertension. Our findings may provide new insights into the cardiovascular protection of telmisartan in hypertensives. © 2011 Published by Elsevier Inc. (Am J Cardiol 2011;107:59–63)

Circulating peripheral monocytes and their activation play an important role in the early and late stages of atherosclerotic lesion formation. Arterial hypertension is accompanied by functional changes in monocytes, promoting expression of adhesion molecules and cytokines, leads to increased monocyte adhesion to the vascular wall,[1] and induces the migration of monocytes/macrophages into the vascular wall in target organs,[2] contributing to the development of atherosclerosis. Antihypertensive medication has been shown to exert beneficial effects in hypertensives often independently of blood pressure (BP) decrease, by inducing several pleiotropic effects. Angiotensin receptor blockers (ARBs) and calcium channel blockers are antihypertensive drugs with established efficacy and a favorable safety profile. We compared the effect telmisartan—an ARB that can partly activate the peroxisome proliferator activated receptor-γ (PPAR-γ)—on monocyte chemoattractant protein-1 (MCP-1) gene expression to amlodipine in peripheral monocytes of patients with essential hypertension. We also examined their effects with respect to expression of the PPAR-γ gene, a nuclear receptor that controls several metabolism-related genes and is involved in various cellular and molecular events such as those related to inflammatory processes.[3]

Methods

Thirty-one patients with mild to moderate hypertension participated in this study. The study population was recruited from the cardiology outpatient department and consisted of subjects who had untreated grade 1 or 2 essential hypertension, with no indications of other organic heart disease. Diagnosis of hypertension was based on 3 outpatient measurements of BP >140/90 mm Hg at intervals ≤2 weeks according to recommendations of the European Society of Hypertension/European Society of Cardiology.[4] Pa-

[a]Cardiology Department, Heraklion University Hospital, Crete, Greece; [b]Kastelli Health Center, Crete, Greece; [c]Division of Biostatistics, University of Crete, Greece. Manuscript received June 10, 2010; revised manuscript received and accepted August 24, 2010.

*Corresponding author: Tel: 30 2810-392422; fax: 30-2810-542055/542111.

E-mail address: cardio@med.uoc.gr (P.E. Vardas).

0002-9149/11/$ – see front matter © 2011 Published by Elsevier Inc.
doi:10.1016/j.amjcard.2010.08.048

tients had not previously taken any hypertensive medication and did not take any other drugs for 3 weeks before the studies. The following were criteria for exclusion: smokers, diabetics, pregnant or lactating women or women potentially childbearing, previous or medication for hypertension, patients with grade 3 hypertension or secondary hypertension, tachyarrhythmias or bradyarrhythmias, coronary artery disease, heart failure, cerebrovascular, liver or renal disease, albumin excretion rate >200 μg/min, history of drug or alcohol abuse, any long-term inflammatory or other infectious disease during the previous 6 months, thyroid gland disease, body mass index >30 kg/m^2, and vascular, metabolic, or neoplastic disease. Patients were randomly assigned to telmisartan (group 1, n = 16) or amlodipine (group 2, n = 15). Medications administered were open-label and initially consisted of telmisartan 40 mg/day or amlodipine 5 mg/day. If systolic BP was >140 mm Hg or diastolic BP was >90 mm Hg after 1 month, the dose was doubled to telmisartan 80 mg or amlodipine 10 mg. BP was measured before and 4, 8, and 12 weeks after treatment. At least 2 measurements were made and mean values of these measurements were used. After enrollment and randomization, a standard echocardiographic study was performed and blood samples were taken for analysis of full clinical chemistry and hematology markers. The same procedure was repeated at the end of the treatment period (12 weeks). In addition, homeostasis model assessment (HOMA) for insulin resistance was calculated each time as fasting blood sugar multiplied by insulin/405. Blood samples were collected into collection tubes containing ethylenediaminetetra-acetic acid. Peripheral blood mononuclear cells were isolated by Histopaque-Ficoll (Sigma, St. Louis, Missouri) centrifugation and CD14$^+$ monocytes were purified from peripheral blood mononuclear cells by positive selection using high-gradient magnetic separation columns (MACS), type MS, and negative magnetic bead selection. Purity assessed by fluorescence-activated cell sorting (FACSCalibur; Becton Dickinson, San Jose, California) analysis was >95%. Total RNA was isolated from monocytes using the TRI Reagent (Ambion, Austin, Texas) and RNA 1 μg was reverse-transcribed with oligo-(dT) using the Reverse Transcription System (Promega, Madison, Wisconsin) in 20-μL reactions. Measurements of mRNA levels were performed by real-time reverse transcription–polymerase chain-reaction using the Stratagene Mx3000P Detection System (Santa Clara, California). Polymerase chain reaction assays were performed in cDNA template 1 μL using the SYBR Green PCR Master Mix (Bio-Rad, Hercules, California). The standard-curve method was used for absolute quantification of amplification products and specificity was determined by performing melting-curve analysis. The housekeeping gene glyceraldehyde-3-phosphate-dehydrogenase (*GAPDH*) was used as an endogenous reference gene. Relative quantification values were normalized to the endogenous reference gene. For each subject, normalized values at follow-up were expressed as fold differences from values before treatment. Primers used were 5′-ATTCCCCAAGGGCTCGCTCA-3′ (sense) and 5′-GCACAGATCTCCTTGGCCACAA-3′ (antisense) for *MCP1*, 5′-AGATGACAGCGAC TTGGCAAT-3′ (sense) and 5′-GGAGCAGCTTGGCAAACAG-3′ (antisense) for *PPAR*-γ, 5′-CCATCTT CCAGGAGCGAG-3′ (sense) and 5′-GCAGGAGGCATTGCTGAT-3′ (antisense) for *GAPDH*. All patients gave written informed consent. The institutional ethics committee approved the study.

Table 1
Baseline data in the two groups

Variable	Amlodipine (n = 15)	Telmisartan (n = 16)
Age (years)	55 ± 8	56 ± 6
Men/women	9/6	10/6
Smokers	9	9
Body mass index (kg/m^2)	27 ± 3	26 ± 3
Fasting glucose (mg/dl)	87 ± 19	97 ± 10
Insulin (IU/ml)	10.6 ± 4.3	11.6 ± 5.1
Homeostasis model assessment for insulin resistance (units)	2.5 ± 1.1	2.8 ± 1.5
Hemoglobin (g/dl)	13.6 ± 1.1	14 ± 0.96
Total cholesterol level (mg/dl)	224 ± 42	227 ± 32
Triglyceride level (mg/dl)	189 ± 87	221 ± 102
Low-density lipoprotein cholesterol level (mg/dl)	143 ± 52	164 ± 63
High-density lipoprotein cholesterol level (mg/dl)	34 ± 40	37 ± 15
Uric acid (mg/dl)	6.7 ± 1.4	5.9 ± 1.8
Treatment with a statin	11	10
Systolic blood pressure (mm Hg)	155 ± 4	157 ± 7
Diastolic blood pressure (mm Hg)	92 ± 4	95 ± 8
Heart rate (beats/min)	68 ± 7	70 ± 4
Ejection fraction (%)	62 ± 5	61 ± 5
Monocyte chemoattractant protein-1 mRNA levels (arbitrary units)	21.4 ± 20.5	12.5 ± 8.5
Peroxisome proliferator-activated receptor-γ mRNA levels (arbitrary units)	29.6 ± 42.5	20 ± 18.5

Summary descriptive statistics are presented as mean ± SD or count (percentage), as appropriate. Continuous variables were compared between the 2 groups by 2-tailed *t* tests or Mann-Whitney tests, as appropriate. Pearson correlation and linear regression was employed to assess the association between continuous parameters. All tests were performed at the 5% level of significance. SPSS 17 (SPSS, Inc., Chicago, Illinois) was used for all analyses.

Results

There was no statistical difference in baseline data between the 2 groups (Table 1). No adverse effects of antihypertensive drugs were noticed. The 2 treatments significantly decreased systolic and diastolic BPs, but there was no significant difference in decrease in BP between the 2 groups. More specifically, amlodipine decreased systolic BP to 139 ± 4 mm Hg and diastolic BP to 87 ± 7 mm Hg (difference in systolic BP 16 ± 3 mm Hg, difference in diastolic BP 6 ± 3 mm Hg, p <0.001 for the 2 comparisons); telmisartan decreased systolic BP to 141 ± 5 mm Hg and diastolic BP to 88 ± 4 mm Hg (difference in systolic BP 15 ± 6 mm Hg, difference in diastolic BP 4 ± 2 mm Hg, p <0.001 for the 2 comparisons). No changes in patients' physical characteristics—body weight or body mass index—were observed at the end of the treatment period (data not shown). However, insulin levels and HOMA were sig-

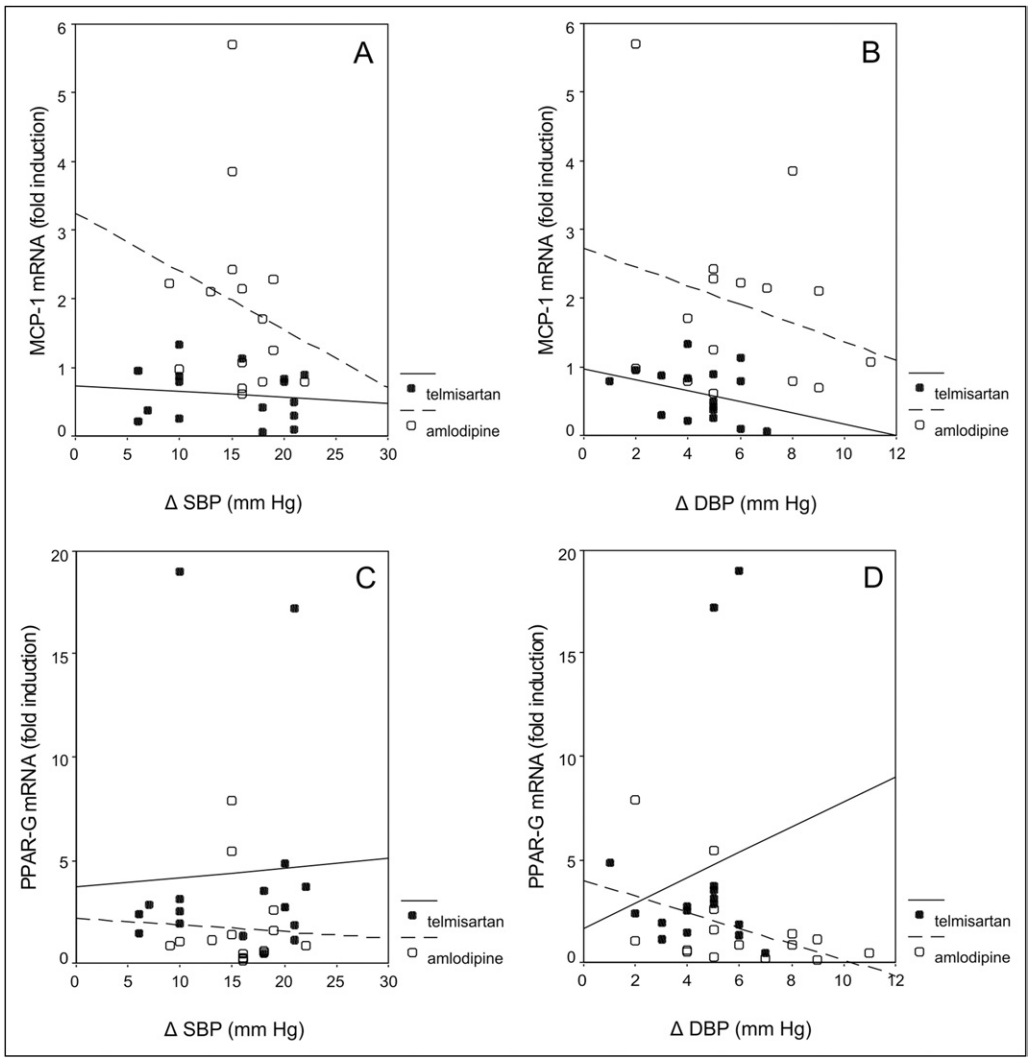

Figure 1. No correlation was found between changes (Δ) in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and fold induction of (*A, B*) monocyte chemoattractant protein-1 and (*C, D*) peroxisome proliferator-activated receptor-γ gene expression in peripheral monocytes in the amlodipine and telmisartan groups.

nificantly improved in the telmisartan group (insulin after treatment 10.8 ± 4.1 IU/ml, p = 0.041, and HOMA after treatment 2.4 ± 1.1, p = 0.028), whereas the amlodipine group did not show any significant change (insulin after treatment 10.6 ± 3.7 IU/mL and HOMA after treatment 2.3 ± 0.9, p = NS for the 2 comparison). In addition, our data showed that treatment with telmisartan significantly downregulated MCP-1 gene expression in peripheral monocytes. MCP-1 mRNA levels decreased significantly to 8.1 ± 6.5 in the telmisartan group (p = 0.009), whereas in the amlodipine group they did not show any significant change during the study period (MCP-1 mRNA levels after treatment 17.6 ± 16.4, p = NS). In addition, PPAR-γ gene expression showed a significant increase in telmisartan-treated patients to 42.6 ± 36 (p = 0.006), but there was no significant change in the amlodipine group (PPAR-γ gene expression after treatment 24.2 ± 27.7, p = NS). Nevertheless, our analysis did not reveal any correlation between changes in systolic and diastolic BPs and fold induction of MCP-1 and PPAR-γ gene expression in the groups of patients we examined (Figure 1).

Discussion

This is the first study to evaluate the effect of telmisartan—an ARB with PPAR-γ agonist activity—on the activation state of peripheral blood monocytes with respect to MCP-1 and PPAR-γ gene expression compared to amlodipine, 1 of the most efficacious calcium channel blockers in patients with essential hypertension. More specifically, our data showed that 3 months of treatment with telmisartan results in a significant attenuation of MCP-1 gene expression and an important upregulation of PPAR-γ gene expression in peripheral monocytes in hypertensives. Although amlodipine was equally effective in decreasing BP, there were no significant effects on any of the studied genes after 3 months of treatment.

ARBs and calcium channel blockers are used extensively in treatment of essential hypertension. Recent studies have

shown that some angiotensin-1 receptor antagonists are able to act as PPAR-γ agonists. Telmisartan exerts this effect even in low concentrations.[5] Telmisartan has a different pharmacokinetic profile compared to other ARBs, and there is a lack of studies examining the effects of an ARB compared to a calcium channel blocker on expression of genes related to monocyte activation in hypertensive patients. We focused on peripheral blood monocytes because arterial hypertension is accompanied by functional changes in monocytes; they are key elements in the pathogenesis of atherosclerosis and are the main participants in hypertension-related atherogenesis.[6] However, data regarding the effect of antihypertensive agents on monocyte activation are lacking. Monocytes are attracted to the place of organ damage by monocyte-specific chemokines and transmigrate from the vascular bed into the tissue,[7] contributing significantly to the pathogenesis of vascular disease. MCP-1—which is 1 of the most prominent chemokines that regulate monocyte–macrophage function—is implicated in hypertensive inflammatory changes in the arterial wall. MCP-1 mediates inflammation and arteriosclerosis, is upregulated, in particular in patients with organ damage,[8] and acts as a central mediator of the inflammatory response in hypertensive vascular disease.[9] Previous studies have shown a decrease of MCP-1 plasma levels after ARB treatment compared to placebo.[10] Our study is the first to examine the effect of ARBs on MCP-1 gene expression in peripheral monocytes and to compare this effect to amlodipine. Endothelial MCP-1 induces vascular inflammation and remodeling, promoting the recruitment of inflammatory cells by the chemokine receptor 2,[11] and overexpression of adhesion molecules and cytokines resulting in intimal hyperplasia and atherosclerosis.[12] Angiotensin II has been directly implicated in the expression of MCP-1 in vascular cells[13] by promoting monocytes to MCP-1 secretion, which plays an essential role in increased inflammation in the vessel.[14] At the molecular level, angiotensin-1 receptor antagonists attenuated the expression of MCP-1 and chemokine receptor 2 in the aorta and peripheral monocytes and lowered the serum level of MCP-1.[15] ARBs have been demonstrated to decrease inflammation by directly blocking the action of angiotensin II.[16] Although the decrease in MCP-1 gene expression in monocytes caused by telmisartan may be attributable directly to inhibition of the effect of angiotensin II, this could also be attributed to PPAR-γ because PPAR-γ agonist has been reported to decrease proinflammatory cytokines in monocytes in experimental studies[17] and has prevented upregulation of MCP-1 receptor expression in lesional and circulating monocytes in animal studies.[18]

In previous studies, telmisartan favorably modulated endothelial inflammation and oxidative cell damage induced by angiotensin II-independent stimuli in cultured human umbilical vein endothelial cell,[19] while it has been shown to decrease serum MCP-1 levels significantly in animal studies.[20] Our findings are in accordance with a previous study showed a more favorable effect of telmisartan compared to amlodipine on inflammation, as indicated by serum levels of IL-6—a proinflammatory cytokine—in untreated hypertensives with chronic kidney disease.[21] Nevertheless, ARB therapy is particularly effective in preventing atherosclerosis. Losartan has also been found to have favorable effects on PPAR-γ[5,22] and some effects on MCP-1[10] and other ARB agents might have similar effects that have not been evaluated. This can be explained to some extent by the fact that angiotensin has several direct and indirect humoral effects that may be implicated in the pathogenesis of atheromatosis. However, telmisartan has protective effects against atherosclerotic damage through its bifunctional effects, that is, a class effect of ARBs and PPAR-γ activation.[23] It has been shown that telmisartan increases the number of regenerative endothelial progenitor cells and improves endothelial function and repair.[24] All these effects are probably inter-related and can explain, at least in part, why telmisartan has beneficial cardiovascular effects that are independent of its BP-lowering action. In contrast, the antiatherosclerotic effect of calcium channel blockers remains controversial.[25] It appears that the reversing of endothelial dysfunction and the pleiotropic action of calcium channel blockers are more effective when these blocker are combined with drugs of other categories that have those kind of properties.[26] For telmisartan, we do not know how much the effects we found could have been influenced by coadministration of other drugs.

PPAR-γ, a nuclear receptor, acts as a transcription factor, influencing insulin sensitivity, and participates in inflammatory and vascular injury processes.[27–29] PPAR-γ activity over the monocyte–macrophage system mainly concerns in in vitro monocytes after in vitro stimulation or during transformation of monocytes into macrophages and foam cells.[30,31] Results of PPAR-γ activation seem to be important in atheromatosis because studies have found that pioglitazone prevents coronary arteriosclerosis, and there is evidence that this effect may occur by its anti-inflammatory action on the MCP-1 receptor (chemokine receptor 2) in a rat model.[18] According to existing knowledge, there is no known evidence of antihypertensive treatment on PPAR-γ in peripheral blood monocytes.

The present study was not a blinded study. However, our measurements and analysis were carried out by investigators who were blinded to treatment groups. We did not measure MCP-1 plasma levels. We focused on the effect of antihypertensive treatment on peripheral monocytes and, because MCP-1 can also be produced by other cell lines, plasma levels could not offer much to our study. We cannot rule out the possibility that to a degree our findings show a class effect and not a drug effect. However, previous data were derived from placebo-controlled studies and there is no comparative prospective study involving agents of these 2 groups and evaluating this action. The small number of patients included may have obscured other statistical significances in our analysis.

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