Blood pressure reduction in telmisartan-treated angiotensinogen G-217A polymorphism hypertensive patients: A pilot study

[Reducción de la presión arterial en pacientes hipertensos con polimorfismo de angiotensinógeno G-217A tratados con telmisartán: un estudio piloto]

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Abstract

Context: The angiotensinogen (AGT) G-217A polymorphism has been proved as one factor contributing the susceptibility of hypertension, meanwhile, the effect of this polymorphism to the variability antihypertensive response remains unknown.

Aims: To investigate whether the angiotensinogen (AGT) G-217A polymorphism affects the blood pressure response to telmisartan and valsartan in Indonesian hypertensive patients.

Methods: The blood pressure was measured by ambulatory blood pressure monitoring (ABPM) and plasma angiotensinogen (AGT) levels of telmisartan- and valsartan-treated AGT G-217A polymorphism hypertensive patients (n=46) were analyzed using ELISA at the baseline and 4 months after treatments. Molecular docking was used to predict the interaction between C/EBPα and AGT G-217A polymorphism.

Results: Daytime and 24 hours blood pressure in telmisartan-treated -217 AA/AG patients were significantly lower compared to GG genotype patients. The plasma AGT level in those who had AA/AG genotype and received telmisartan 80 mg was also slightly decreased compared to GG genotype, even these differences were failed to reach statistically significant. The docking results showed that the basic region of C/EBPα transcription factor recognized the partially homologous of its consensus sequences within -217A oligonucleotide, but not in -217G oligonucleotide.

Conclusions: The blood pressure reduction responses in telmisartan-treated angiotensinogen G-217A polymorphism hypertensive patients might correlate with PPARγ agonist effects of telmisartan via C/EBPα and AGT -217A interaction.

Keywords: AGT G-217A polymorphism; hypertension; telmisartan; valsartan.

Resumen

Contexto: El polimorfismo del angiotensinógeno (AGT) G-217A se ha demostrado como un factor que contribuye a la susceptibilidad de la hipertensión, mientras tanto, el efecto de este polimorfismo sobre la variabilidad de la respuesta antihipertensiva permanece desconocido.

Objetivos: Investigar si el polimorfismo angiotensinógeno (AGT) G-217A afecta la respuesta de la presión arterial a telmisartán y valsartán en pacientes hipertensos indonesios.

Métodos: Se realizó la monitorización ambulatoria de la presión arterial (MAPA) y se analizaron los niveles de angiotensinógeno plasmático (AGT) de pacientes hipertensos con polimorfismo AGT G-217A tratados con telmisartán y valsartán (n=46), mediante ELISA, al inicio y 4 meses después de los tratamientos. El acoplamiento molecular se usó para predecir la interacción entre el polimorfismo C/EBPα y AGT G-217A.

Resultados: La presión arterial durante el día y las 24 horas en pacientes -217 AA/AG tratados con telmisartán fueron significativamente menores en comparación con los pacientes con genotipo GG. El nivel de AGT en plasma en aquellos que tenían genotipo AA/AG y recibieron 80 mg de telmisartán también se redujo ligeramente en comparación con el genotipo GG, incluso estas diferencias no fueron estadísticamente significativas. Los resultados de acoplamiento mostraron que la región básica del factor de transcripción C/EBPα reconocía el homólogo parcialmente se su secuencia de consenso en el oligonucleótido -217A, pero no en el oligonucleótido -217G.

Conclusiones: Las respuestas de reducción de la presión arterial en pacientes hipertensos con polimorfismo de angiotensinógeno G-217A tratados con telmisartán podrían correlacionarse con los efectos del agonista de PPARγ de telmisartán via interacción C/EBPα y AGT-217A.

Palabras Clave: hipertensión; polimorfismo AGT G-217A; telmisartán; valsartán.

INTRODUCTION

Hypertension is a major health problem worldwide. It has been reported that despite the wide availability of antihypertensive drugs, only one to three patients had controlled blood pressure after therapy (Rahimi et al., 2015; Mills et al., 2016). Even though many factors contribute to the high numbers of uncontrolled patients, evidence suggest that there is a huge inter-individual response to antihypertensive therapy that might be attributable to genetic variations (Johnson, 2012; Fontana et al., 2015).

The renin angiotensinogen aldosterone system (RAAS) regulates blood pressure and fluid homeostasis. It is well established that single nucleotide polymorphisms (SNPs) within this system correlate with hypertension susceptibility (Zhu et al., 2003; He et al., 2015) Angiotensinogen (AGT) is a precursor of angiotensin II (AngII). It is encoded by AGT gene on chromosome 1 and mainly synthesized in the liver. It is cleaved by renin then converted to AngII by angiotensin-converting enzyme (ACE). The renin-AGT reaction is the rate-limiting step of RAAS. Of note, the AGT level is a crucial determining factor for hypertension development. In several studies, increased AGT level causes by AGT G-217A single nucleotide polymorphism (SNP) consequently causes hypertension (Jain et al., 2002; 2008).

Interestingly, several genetic variants of AGT are also associated with inter-individual variation in response to RAAS blockade therapy (Kurland et al., 2004; Santos et al., 2012; Do et al., 2014). Angiotensin II type I receptor blockers (ARBs) has become a cornerstone of blood pressure-lowering therapy. Telmisartan and valsartan are commonly used ARBs in the management of hypertension. Many studies prove the efficacy of telmisartan and valsartan (Nixon et al., 2009; Zheng et al., 2010; Marfatia et al., 2012). However, limited studies have investigated the effects of AGT G-217A on telmisartan and valsartan response.

This study demonstrated the variability antihypertensive response in telmisartan-treated angiotensinogen G-217A polymorphism, but not valsartan-treated hypertensive patients. The distinct conformational C/EBP-oligonucleotides containing -217G or -217A allele might be a potential mechanism that could explain the variability antihypertensive response to these drugs.

MATERIAL AND METHODS

Subjects

Forty-six hypertensive outpatients from cardiology department of Dr. Saiful Anwar Hospital, 23 patients received telmisartan 80 mg and 23 patients received valsartan 160 mg were enrolled and followed up for four months. The inclusion criteria were aged <65 years, had a systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg and/or never received with drawl of ARB for at least 1 week. Patients with hepatic and renal failure, pregnancy and patients with known estrogen and corticosteroid therapy were excluded. Informed consent was obtained from each patient. The experiments were performed in accordance with the ethical principles for medical research outlined in the Declaration of Helsinki 2008. This study was approved by the committee ethic for research on human subjects in the medical faculty of Brawijaya University (Approval number: 332/KEPK/VI/2012).

Blood pressure and plasma angiotensinogen (AGT) protein measurement

Blood pressure was measured using ABPM device as the mean of daytime (6 a.m. to 10 p.m.), night-time (10 p.m. to 6 a.m.), and 24 hours at baseline and after four-month ARB treatment.

The venous blood sample was collected after 20 minutes of rest in a supine position at baseline and after ARB treatment for four months. Plasma AGT concentration was measured by ELISA using Cusabio Human Angiotensinogen Elisa Kit (CSB-E08564h), as previously described by Mao et al. (2012).
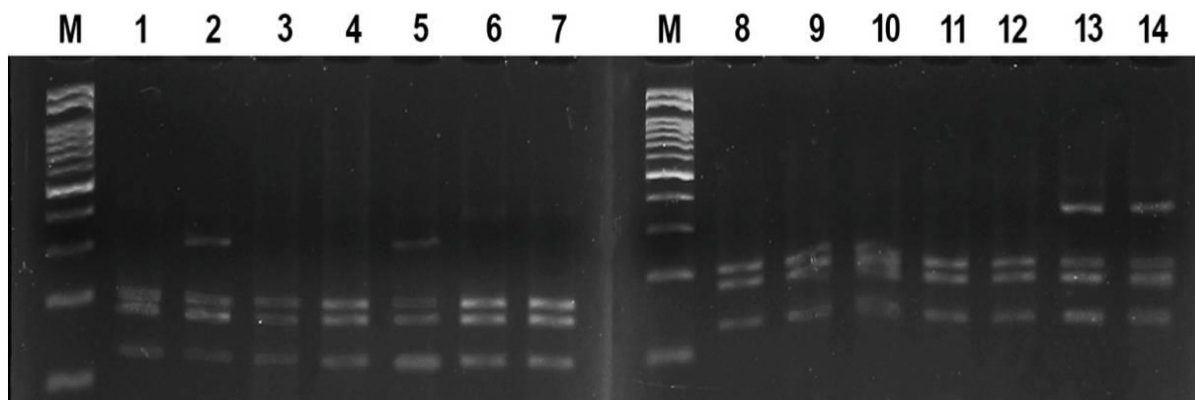
Figure 1. Agarose gel electrophoresis of PCR-RFLP products of AGT *G-217A* (rs5049) polymorphism.

Marker (M): 1 kb. Lane 1, 3, 4, 6-12 are homozygous GG. Lane 2, 5, 13, 14 are heterozygous AG.

Genotyping

Genomic DNA was extracted from the venous blood samples using Invitrogen Purelink Genomic DNA Kits. Genotyping of the AGT G-217A gene polymorphism (rs5049) was performed using PCR/restriction fragment length polymorphism (RFLP)-based technique as described in Woodiwiss et al. (2006). Briefly, the amplified of 593 bp fragment of the 5' untranscribed region were obtained after 3 mins of denaturation at 95°C, 35 cycles for 30 secs at 95°C, 30 secs at 60°C, 30 secs at 72°C, and 10 mins of final extension at 72°C. Ten microliters of the PCR product were digested with 2 U of MspI (Thermo Scientific). The -217 G allele was presented on 2% agarose as 207, 181, and 128 bp bands, whereas A allele as 335 and 181 bp bands, shown in Fig. 1. The accuracy of genotyping was confirmed with direct sequencing techniques using ABI PRISM 3730xl Genetic Analyzer (Applied Biosystems, USA) as shown in Fig. 2.

Docking procedure

A double-stranded 22 bp oligonucleotides (-229 to -208) containing -217G allele (CGACCCTG-CACCGGCTCACTCT) and -217A allele (CGACCCTGCACCAGCTCACTCT), as previously described Jain et al. (2002), were built using 3D-DART provided by HADDOCK (http://haddock.science.uu.nl/services/3DDART/). The 3D Model of C/EBPα was obtained from the RCSB protein data bank (http://www.rcsb.org/pdb/home/home.do).

The prediction of consensus DNA-C/EBPα interaction binding site was predicted using DISPLAR. The amino acid that involved in C/EBPα (basic region) – DNA was N281, S282, N283, E284, Y285, R286, V287, R288, R289, E290, R291, N292, N293, I294, A295, V296, R297, K298, S299, R300, D301, K302, A303, K304, Q305, R306. The C/EBPα and -217G/A oligonucleotides were docked using the docking program PATCHDOCK (http://bioinfo3d.cs.tau.ac.il/PatchDock/). The best 10 solutions were selected by FIREDOCK. The visualization was done by PyMol. The difference amino acid-nucleotides interface between these two oligonucleotides were visualized using NUCPLOT.

Statistical analysis

The statistical tests were performed using the IBM SPSS Statistics version 20.0. The numeric variables are reported as the mean ± standard deviation. Log transformation of plasma AGT concentration was performed to improve normality of the data. Differences of the mean were evaluated by Student's t-test for normal continuous distribution variables, or by a non-parametric test for non-normal distribution. A 2-tailed $p<0.05$ were considered statistically significant. The docking procedure was descriptively analyzed.
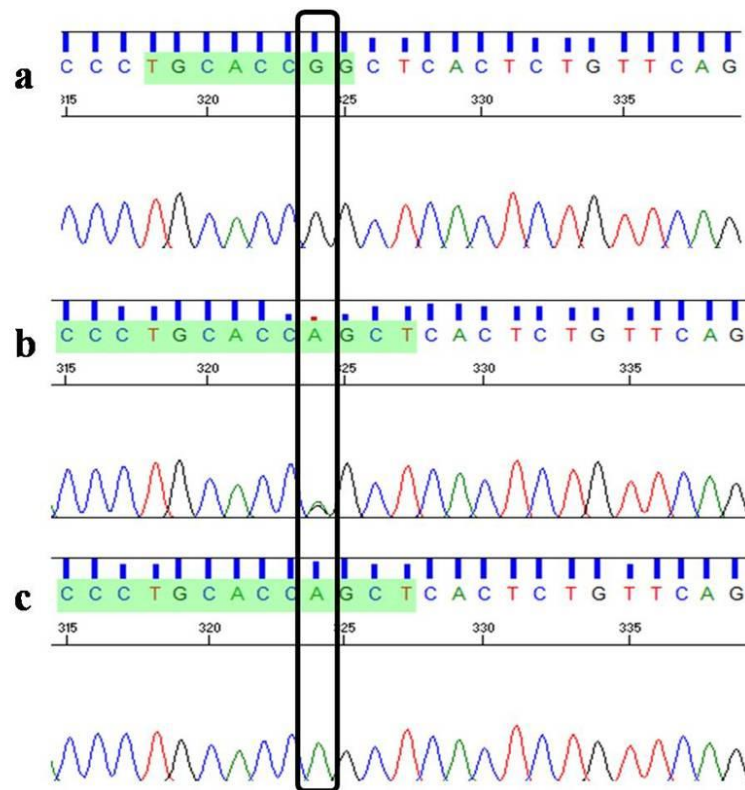
Figure 2. AGT G-217A (rs5049) polymorphism by direct sequencing.

Box represents the location of G/A transition at base -217 AGT. **(a)** represents homozygous GG,
(b) heterozygous AG, and **(c)** homozygous AA.

RESULTS

Distribution of angiotensinogen G-217A polymorphism variation

Of the 46 participants, only one who has an AA genotype. The genotype frequencies in both groups were 78.3% for GG genotype, 19.6% for AG genotype, and 2.1% for AA genotype. The allele frequencies were 88% for G allele and 12% for A allele.

Baseline and clinical characteristics

The baseline and clinical characteristics of AG/AA genotype and GG genotype patients are summarized in Table 1. A total of 46 hypertensive patients were enrolled in our study, five patients had AA/AG genotype, and 18 patients had the GG genotype in either telmisartan 80 mg or valsartan 160 mg group. No statistically significant ob-

served in baseline characteristic between telmisartan and valsartan group.

In telmisartan-treated hypertensive patients, but not valsartan, daytime and 24-hours reduction of SBP and DBP were significantly higher in those who had AA/AG genotype than GG genotype. Meanwhile, the mean of changed night-time SBP and DBP in both groups were no difference (Table 1). The plasma AGT level in those who had AA/AG genotype and received telmisartan 80 mg was also slightly decreased compared to the GG genotype, although these differences were failed to reach statistically significant.

C/EBPα and DNA docking

The docking analysis was performed to explain this response difference. The C/EBPα was chosen as a candidate molecule since it is known to bind to -217 of angiotensinogen promoter site (Jain et

Table 1. Clinical characteristic of study participants.

	Telmisartan 80 mg (n=23)			Valsartan 160 mg (n=23)		
	GG (n=18)	AG/AA (n=5)	P value	GG (n=18)	AG/AA (n=5)	P value
Age (years)	57.2 ± 8.2	55 ± 5.9	0.591	60.8 ± 9.7	55.6 ± 9.4	0.300
Male (%)	61.1	60	1.000	44.4	40.0	1.000
Urea (mg/dL)	27.2 ± 8.9	29.8 ± 11.2	0.823	27.2 ± 7.9	21.9 ± 8.1	0.200
Creatinine (mg/dL)	1.02 ± 0.2	0.92 ± 0.3	0.445	1.0 ± 0.3	0.9 ± 0.1	0.565
Changed daytime SBP (mmHg)	0.3 ± 11.9	-16.7 ± 13.5	0.012*	-9.4 ± 14.5	-15.2 ± 8.9	0.502
Changed daytime DBP (mmHg)	-0.1 ± 9.3	-10.9 ± 10.2	0.034*	-5.4 ± 8.3	-9.7 ± 5.4	0.293
Changed night-time SBP (mmHg)	-3.1 ± 13.6	-15.5 ± 12.7	0.081	-8.9 ± 15.3	-14.1 ± 20.6	0.543
Changed night-time DBP (mmHg)	-2.2 ± 10.3	-10.5 ± 6.4	0.107	-4.9 ± 8.3	-12.3 ± 12.6	0.131
Changed 24 hours SBP (mmHg)	-0.9 ± 11.6	-16.3 ± 12.4	0.017*	-9.3 ± 14.1	-14.9 ± 11.5	0.422
Changed 24 hours DBP (mmHg)	-0.8 ± 9.1	-10.7 ± 8.6	0.040*	-5.5 ± 7.5	-10.3 ± 6.9	0.209
Changed AGT plasma level (µg/mL)	61.4 ± 125.9	-33.9 ± 163.1	0.173	21.2 ± 156.9	24.1 ± 87.3	0.969

SBP: systolic blood pressure; DBP: diastolic blood pressure; AGT: angiotensinogen. Values are given as mean ± SEM; *$p<0.05$ represent statistical differences between GG and AG/AA genotype in both telmisartan and valsartan groups.

al., 2002; 2008). A coiled-coil dimer structure of C/EBPα contains three domains, i.e., leucine zipper, basic region, and extended basic region. The basic region of C/EBPα was docked onto each oligonucleotide which contains -217G allele or -217A allele. The docking results showed that the basic region of C/EBPα recognized the partially homologous of its consensus sequences within -217A oligonucleotide, but not in -217G oligonucleotide, described in Fig. 3. The adenine at -217 position provided a hydrogen bond with asparagine (Asn292) of C/EBPα. Furthermore, we analyzed that the interaction of Asn292 of C/EBPα with -217A was favored amino acid-base hydrogen bonds.

DISCUSSION

In this study, we found that AGT G-217A contribute to the favorable antihypertensive response of telmisartan-treated group, but not valsartan-treated group. To further explore the possible mechanism of the difference we analyzed that -217 AGT supposed to be a promoter region recognized by C/EBPα transcription factor. C/EBPα is a family member of basic region leucine zipper (bZIP) transcription factors that regulate some genes expression. The binding specificity of C/EBPα to its consensus has been studied widely (Miller et al., 2003). However, C/EBPα frequently binds to promoters containing non-canonical C/EBP sites, such as an oligonucleotide containing angiotensinogen G-217A polymorphism (Jain et al., 2002; 2008). Angiotensinogen G- 217A polymorphism provides a partial homology of consensus C/EBPα at position -225 to -216 with one mismatch at position -224 or position (-4) on consensus C/EBPα binding site, described in Fig. 3. We found a distinct conformational change of the interaction between C/EBPα and oligonucleotides containing -217G or -217A allele. Adenine at position -217 formed a hydrogen bond to Asn292 of C/EBPα, which is involved in stabilizing interaction for DNA binding affinity, see Fig. 3. This interaction was favored amino acid-base hydrogen bonds (Luscombe et al., 2001). On the other hand, oligonucleotides containing -217G form a symmetrical

mismatch, described in Fig. 4, which might explain why C/EBPα failed to dock on. In line with this finding, Jain et al. (2002) also demonstrated that C/EBPα dock more strongly on oligonucleotides containing -217A compared to -217G. Recently, Vernochet et al. (2009) also described the repression of resistin and angiotensinogen expression involves recruitment of two co-repressors, CtBP1/2, directed by C/EBPα, to their promoters in response to PPARγ agonists. This evidence suggested that peroxisome proliferator-activated–γ (PPARγ) reduce angiotensinogen gene expression, at least in part, via C/EBPα- 217A AGT interaction.
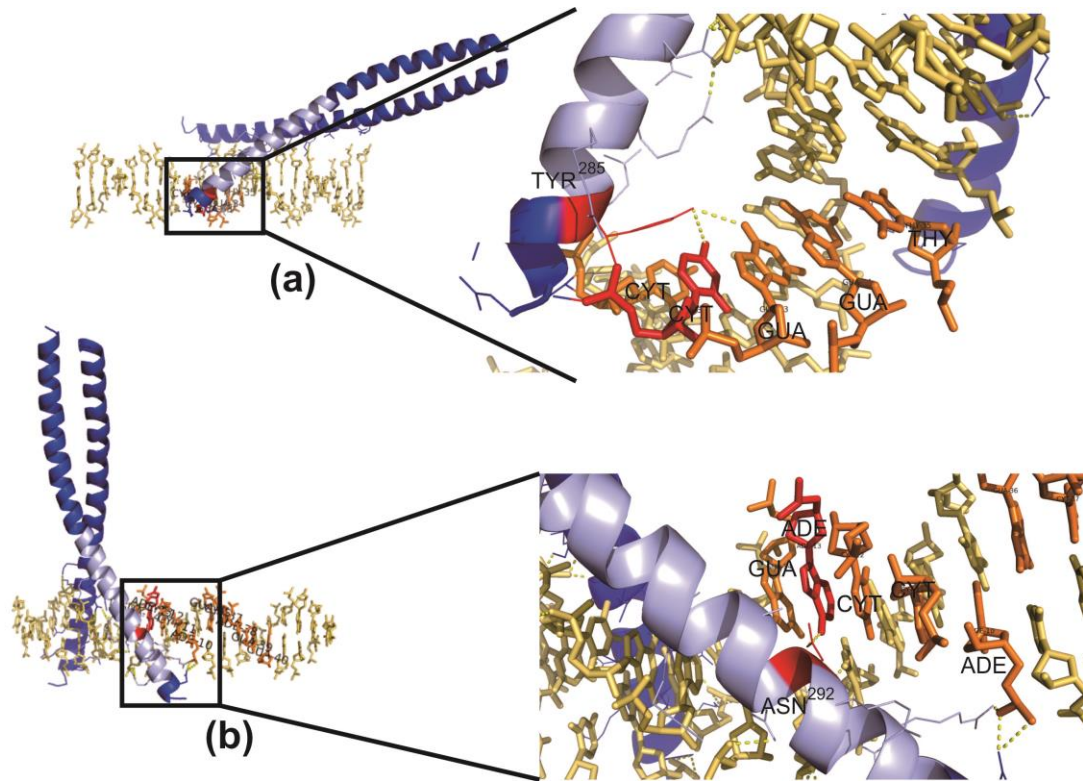
Figure 3. The visualization of C/EBPα-DNA interface.

(a) the C/EBPα and oligonucleotides containing -217G allele. The basic region domain (light blue) of C/EBPα failed to recognise the DNA binding site. **(b)** the C/EBPα and oligonucleotides containing -217A allele. The basic region domain (light blue) of C/EBPα recognised the DNA binding site, which has partially homologous of its consensus binding site due to adenine in position -217. Red in double helix DNA shown position -217. Red in coiled-coil C/EBPα structure (light blue) shown the amino acid that involved in the C/EBPα-DNA interface in position -217. Orange in double helix DNA shown the sequences that partially homologous between human angiotensinogen promoter and the consensus of C/EBPα binding site, as described in Jain et al. (2002).
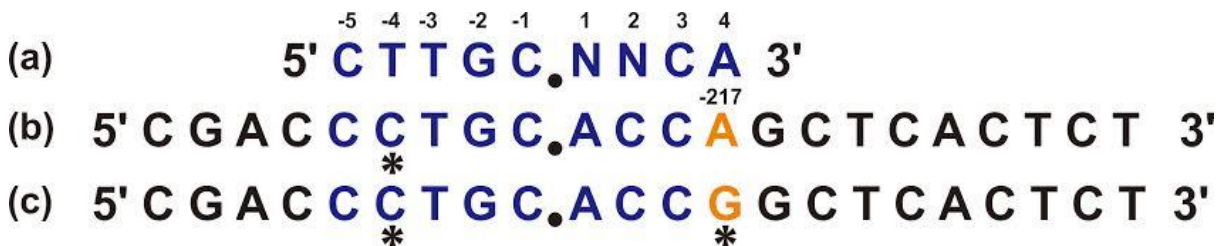
Figure 4. The consensus binding of C/EBPα.

(a) The consensus binding of C/EBPα (blue), as described previously (Jain et al. 2002); **(b)** The 22 bp oligonucleotides in promoter angiotensinogen containing -217A (orange); **(c)** The 22 bp oligonucleotides in promoter angiotensinogen containing -217G (orange).

The previous study also reported that telmisartan has been known to activate PPARγ partially, whereas valsartan has no PPARγ activating effect (Benson et al., 2004; Schupp et al., 2004; Erbe et al., 2006; Goyal et al., 2011; Kakuta et al., 2014). Therefore, we suggest that the variability of the blood pressure reduction response in telmisartan-treated, but not valsartan-treated, might correlate with PPARγ agonistic effects. As a new selective PPAR modulators (SPPARMs), telmisartan has been proved that elicits similar effects with full PPARγ agonist in regulating PPARγ-modulated genes expressions, such as resistin and angiotensinogen (Schupp et al., 2005).

It is well accepted that the changes in angiotensinogen expression may also influence systemic blood pressure (Kobori et al., 2007; Santos et al., 2012; Gudo et al., 2014). Lower plasma angiotensinogen level was found on those who had AG/AA genotypes compared with GG genotypes in the telmisartan-treated group, but not in valsartan, although these findings failed to reach a statistically significant (may because of small sample size). In line with the changes in angiotensinogen expression, the variability anti-hypertensive response among the AGT G-217A polymorphism hypertensive patients occurred only in the telmisartan-treated group. These data support the blood pressure reduction response in telmisartan-treated may correlate with the changes in angiotensinogen expression due to PPARγ agonistic effects.

These findings might explain the significantly lower changed daytime and 24-hours SBP and DBP as well as slightly lower plasma angiotensinogen level in telmisartan-treated angiotensinogen G-217A polymorphism in hypertensive patients.

In the present study, no data is explaining the variability blood pressure reduction that only occurs in the daytime, but not night time. This data may be related to administration of telmisartan at night. Therefore, some larger subject studies are also needed to validate this finding.

CONCLUSIONS

Blood pressure reduction responses in telmisartan-treated angiotensinogen G-217A polymorphism hypertensive patients might correlate with PPARγ agonist effects of telmisartan via Asn292 of C/EBPα – 217A angiotensinogen gene interaction.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Contribution	Rohman MS	Ramadhiani R	Widodo W	Putri VYGS	Lukitasari M	Putri JF	Utomo DH
Concepts or ideas	x		x				
Design	x	x	x				
Definition of intellectual content	x		x				
Literature search		x		x	x		
Clinical studies				x	x		
Experimental studies		x				x	x
Data acquisition		x				x	x
Data analysis	x	x	x	x	x	x	x
Statistical analysis	x	x	x		x		
Manuscript preparation	x	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x

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