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ORIGINAL ARTICLE

Effects of telmisartan on the cerebral circulation of hypertensive patients with chronic-stage stroke

This article has been corrected since Advance Online Publication, and a corrigendum is also printed in this issue.

Ichiro Deguchi, Daisuke Furuya, Takuya Fukuoka and Norio Tanahashi

This prospective study examined the effects of telmisartan, an angiotensin II type I receptor blocker with peroxisome proliferator-activated receptor gamma agonistic action, on blood pressure (BP) control and cerebral circulation in hypertensive patients with chronic-stage stroke. Telmisartan (40 mg per day) was administered to 10 patients with systolic BP (SBP) ⩾140 mm Hg and diastolic BP (DBP) ⩾90 mm Hg at least 4 weeks after lacunar or atherothrombotic infarction. Casual BP and resting cerebral blood flow (CBF) were evaluated at baseline and week 12 using technetium-99 m ethyl cysteinate dimer single-photon emission computed tomography. Both SBP and DBP declined significantly from 156.4 ± 17.0 to 127.4 ± 6.6 mm Hg and 84.2 ± 14.5 to 74.2 ± 5.2 mm Hg, respectively ($P<0.05$). Mean CBF (mCBF) in both the left and right cerebral hemispheres did not change, and the mCBF of both the impaired and unimpaired sides of supratentorial lesion patients ($n=6$) did not change. Investigation of regional CBF in all patients revealed significant increases in the callosomarginal, precentral, central, parietal, temporal, posterior cerebral, lenticular nucleus, thalamic and hippocampal regions at week 12 ($P<0.05$). Telmisartan showed good antihypertensive activity in hypertensive patients with chronic-stage stroke without affecting hemispheric blood flow, and it even increased regional CBF in most regions examined.
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Keywords: cerebral blood flow; chronic-stage stroke; peroxisome proliferator-activated receptor gamma (PPARγ) agonist; telmisartan

INTRODUCTION

In patients with a history of stroke, hypertension represents the greatest risk factor for stroke recurrence.[1] Therefore, blood pressure (BP) control is essential in the treatment of patients with chronic-stage stroke. The Japanese Guidelines for the Management of Stroke recommend a systolic BP/diastolic BP (SBP/DBP) target of <140/90 mm Hg for chronic-stage stroke patients.[2] Several large-scale clinical studies have demonstrated that angiotensin II type I receptor blockers (ARBs) in particular are very effective antihypertensive agents in secondary, as well as primary, stroke prevention.[3–5] In addition to their antihypertensive action, ARBs are also noted for their effects on the cerebral circulation. Several studies have described the effects of the ARBs losartan, valsartan and olmesartan in maintaining and increasing cerebral blood flow (CBF) and improving cerebral perfusion reserve capacity in chronic-stage stroke patients.[6–9] Although previous studies on telmisartan have reported reduced infarct size[10–12] and increased CBF[13] in mouse and rat cerebral ischemia models, there have not been any clinical studies on the effects of telmisartan on cerebral circulation in chronic-stage stroke patients.

In the present study, the effects of telmisartan, an ARB with peroxisome proliferator-activated receptor gamma (PPARγ) agonist action, on BP control and cerebral circulation were prospectively examined in hypertensive patients with chronic-stage stroke.

METHODS

The patients' demographics are shown in Table 1. The subjects were 10 hypertensive (⩾140/90 mm Hg) patients (six men and four women; mean age ± s.d.: 64 ± 6.8 years) who had suffered a lacunar or atherothrombotic stroke at least 4 weeks prior and had provided their written, informed consent to participate in the study. Exclusion criteria were: (1) concomitant atrial fibrillation, (2) pregnancy or possibility of pregnancy, (3) serious biliary excretion dysfunction (⩾2.0 mg dl^{-1}) or hepatic/renal disorder (aspartate aminotransferase or alanine aminotransferase ⩾100 IU l^{-1}; Cr ⩾3.0 mg dl^{-1}), (4) hyperkalemia, (5) current treatment with antihypertensive agents or pioglitazone and (6) history of allergy to ARBs. Seven patients had lacunar infarcts (four supratentorial and three subtentorial) and three patients had atherothrombotic infarcts (two supratentorial and one subtentorial). Magnetic resonance angiography findings of main trunk lesions were seen in two patients with left middle cerebral artery stenosis and one patient with left vertebral artery occlusion. After measuring casual BP and CBF in the sitting position at least 4 weeks after stroke onset, oral treatment with 40 mg once daily of telmisartan was started on the same day. If patients had not reached the BP-reduction goal (SBP <140 mm Hg or DBP <90 mm Hg) at week 4, the dosage was increased to 80 mg per day. BP and CBF were measured again at

Department of Neurology and Cerebrovascular Medicine, International Medical Center, Saitama Medical University, Hidaka, Hidaka, Japan
Correspondence: Dr I Deguchi, Department of Neurology and Cerebrovascular Medicine, Saitama International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka 350-1298, Japan.
E-mail: ideguchi@saitama-med.ac.jp
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Table 1 Patient's clinical characteristics

Case number	Age (years)/ sex	Clinical type	Site of infarction	Major artery lesion on MRA	Time from onset to beginning of telmisartan (days)	Telmisartan dose (mg per day)	Hypertension	Diabetes	Hyperlipidemia
1	76/M	LC	Pons (Rt)	—	32	40	+	+	+
2	57/M	LC	Medulla (Rt)	—	30	40	+	−	+
3	65/M	LC	Pons (Rt)	—	30	40	+	−	+
4	67/F	AT	Temporal-parietal (Lt)	Lt.M1-s	71	40	+	−	−
5	69/M	LC	Corona radiata (Rt)	—	30	40	−	+	−
6	54/F	LC	Lentiform nucleus-corona radiata (Rt)	—	36	40	+	+	−
7	67/F	AT	Temporal-parietal (Lt)	Lt.M2-s	29	40	+	+	+
8	59/F	AT	Cerebellum (Lt)	Lt.VA-o	40	40	+	+	+
9	59/M	LC	Lentiform nucleus (Rt)	—	29	40→80	+	−	−
10	69/M	LC	Thalamus (Rt)	—	32	40	+	−	−

Abbreviations: AT, atherothrombotic infarction; F, female; LC, lacunar infarction; Lt, left; M, male; M1 · 2-s, middle cerebral artery M1 segment, M2 segment stenosis; MRA, magnetic resonance angiography; Rt, right; VA-o, vertebral artery occlusion.

week 12. The mean time from stroke onset to commencement of telmisartan therapy was 36 ± 13 days. The daily dosage was increased to 80 mg in one patient. Measurement of CBF was performed at baseline and week 12 using single-photon emission computed tomography (Symbia T6; Siemens AG, Munich, Germany) technetium-99 m ethyl cysteinate dimer was used as the tracer, and mean CBF (mCBF) was determined based on Patlak plot analysis. Regional CBF of 12 segments (callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus and cerebellar hemispheric) was calculated using a three-dimensional stereotaxic region of interest (ROI) template.

This study was approved by the Institutional Review Board at the Saitama Medical University International Medical Center.

Statistical analysis

Statistical analysis of data was performed using PASW statistics software (Version 18; SPSS, Inc., Chicago, IL, USA). Changes in BP and CBF before and after telmisartan therapy were tested using the Wilcoxon signed-rank test. For each analysis, a *P*-value <0.05 was considered a significant difference.

RESULTS

Changes in BP before and after treatment with telmisartan are illustrated in Figure 1. Both SBP and DBP declined significantly from 156.4 ± 17.0 to 127.4 ± 6.6 mm Hg and 84.2 ± 14.5 to 74.2 ± 5.2 mm Hg, respectively ($P<0.05$). No paralysis or other deterioration in clinical symptoms was observed during the study. Changes in mCBF before and after treatment with telmisartan are shown in Figures 2 and 3. The mCBF in both the left and right cerebral hemispheres did not change, and the mCBF of both the impaired and unimpaired sides of the six supratentorial lesion patients did not change. Investigation of regional CBF in all patients revealed significant increases at week 12 in the callosomarginal (44.0 ± 4.8 to 46.6 ± 6.3), precentral (43.7 ± 5.1 to 46.1 ± 6.2), central (44.0 ± 4.4 to 46.1 ± 5.7), parietal (43.3 ± 4.0 to 45.0 ± 5.4), temporal (43.0 ± 4.9 to 44.1 ± 5.6), posterior cerebral (43.0 ± 4.5 to 55.3 ± 5.9), lenticular nucleus (50.1 ± 5.7 to 53.1 ± 7.1), thalamus (38.4 ± 6.6 to 40.6 ± 7.2) and hippocampus (36.0 ± 5.6 to 38.4 ± 4.0) regions ($P<0.05$).

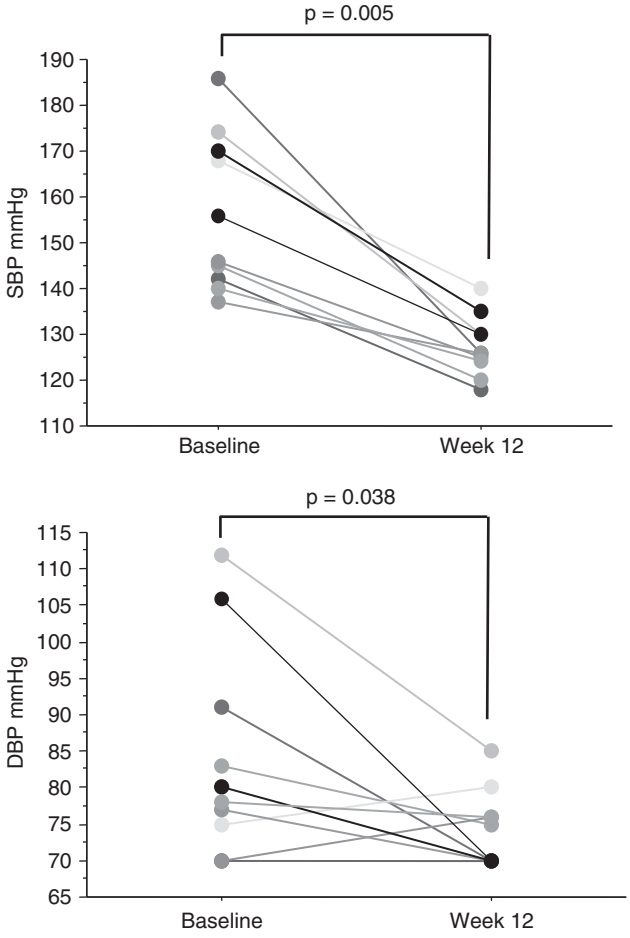

Figure 1 Change in BP before and after telmisartan therapy Both SBP and DBP decrease significantly after 12 weeks of therapy. A full color version of this figure is available at the *Hypertension Research* journal online.

DISCUSSION

The findings of the present study showed that, although telmisartan therapy had a sufficient hypotensive action on hypertensive patients with chronic-stage stroke, CBFs were maintained in the cerebral hemispheres and did not decline, even on the infarct side. Examination of CBF by region also indicated increases in most regions. The mechanism behind this sustained CBF despite the decline in BP is

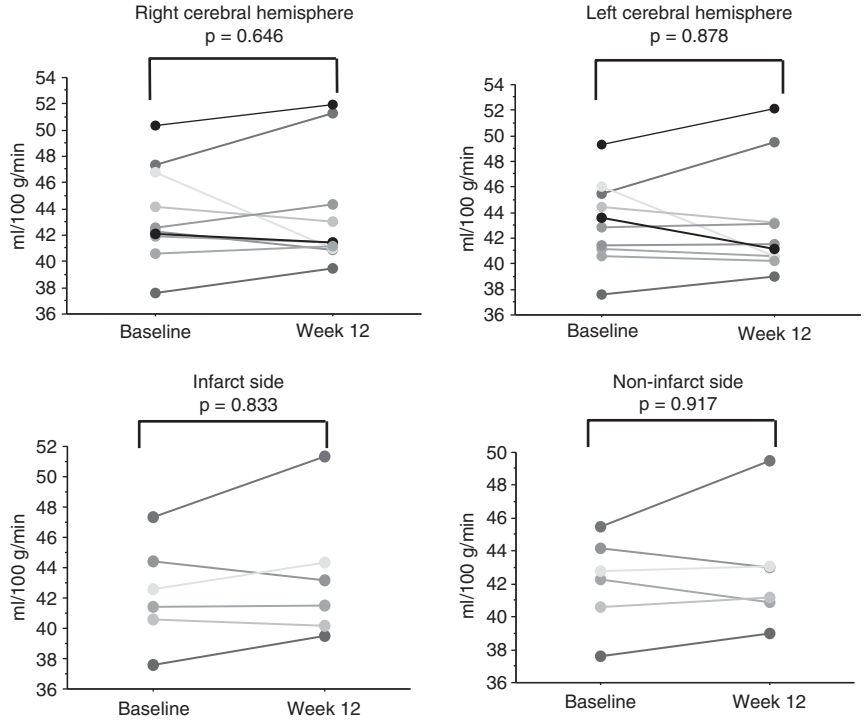

Figure 2 Change in mCBF before and after telmisartan therapy. Upper graphs: No significant changes in mCBF are observed in either the left or right cerebral hemisphere after 12 weeks of therapy. Lower graphs: No significant changes in mCBF are observed in either the infarct or non-infarct side after 12 weeks of therapy. A full color version of this figure is available at the *Hypertension Research* journal online.

thought to involve the PPARγ agonist action of telmisartan, as well as its effects as an ARB.[14,15]

The angiotensin II receptor-blocking effects of telmisartan include its action on autoregulation of cerebral circulation. This autoregulation function is known to shift rightwards in hypertensive patients. It has been suggested that, in hypertensive animal models, telmisartan causes a leftward shift in the autoregulation curve similar to that of candesartan and varsartan, thus enabling CBF to be maintained even in a hypotensive state,[16–19] and this was also considered to be a factor in maintaining CBF in the present study.

An additional mechanism of telmisartan is its effect on the vascular endothelium. A study of hypertensive rats by Saavedra *et al.*[20] found that blockade of AT1 receptors increases expression of AT2 receptors, leading to enhanced endothelial nitric oxide synthase activity and nitric oxide production in vascular endothelium. Meanwhile, Nagata *et al.*[21] reported that olmesartan therapy in elderly patients with hypertension improved cerebral hypoperfusion by boosting nitric oxide concentration. Telmisartan, with its high AT1 receptor affinity, likely exhibited this same mechanism to maintain and increase CBF in the present study. In addition to its AT1 receptor-blocking action, telmisartan is also thought to have changed cerebral perfusion due to its PPARγ agonist action. In two separate studies on the effects of telmisartan therapy on cerebrovascular blood flow in mice, the activation of PPARγ by telmisartan was partly responsible for the resultant increase in cerebral perfusion due to its beneficial effect on vascular endothelial function, which in turn enhanced endothelial synthesis of nitric oxide.[11,22] Administration of pioglitazone, another PPAR-γ agonist, reportedly improved pulsatility index (cerebrovascular resistance) and CBF.[23,24] As an ARB with particularly high lipid solubility and PPARγ-activating effects, telmisartan is therefore capable of significantly influencing CBF, given its outstanding ability to penetrate the blood–brain barrier. Telmisartan is also said to help restore the vascular structure (restoration of vascular remodeling) by inhibiting superoxides,[19] and this action was also thought to have a part in sustaining and increasing CBF in the present study.

A recent study has also reported that ARBs have a beneficial effect on cognitive function.[25] Kume *et al.*[26] demonstrated that telmisartan improved cognitive function in Alzheimer's disease patients with hypertension more than amlodipine, although the difference was not significant, whereas Imabayashi *et al.*[27] found that it controlled declining glucose metabolism in the olfactory tract of patients with Alzheimer's disease. The present study did not undertake a detailed investigation of cognitive and other higher-order brain functions. Accordingly, it is possible that improvement in higher-order brain function resulting from telmisartan therapy may have influenced the single-photon emission computed tomography findings of sustained cerebral hemispheric perfusion and increased regional flows. Small sample size and the lack of other clinical evaluations, such as of higher-order brain function, were limitations of the present study. Further study based on a large number of patients is warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

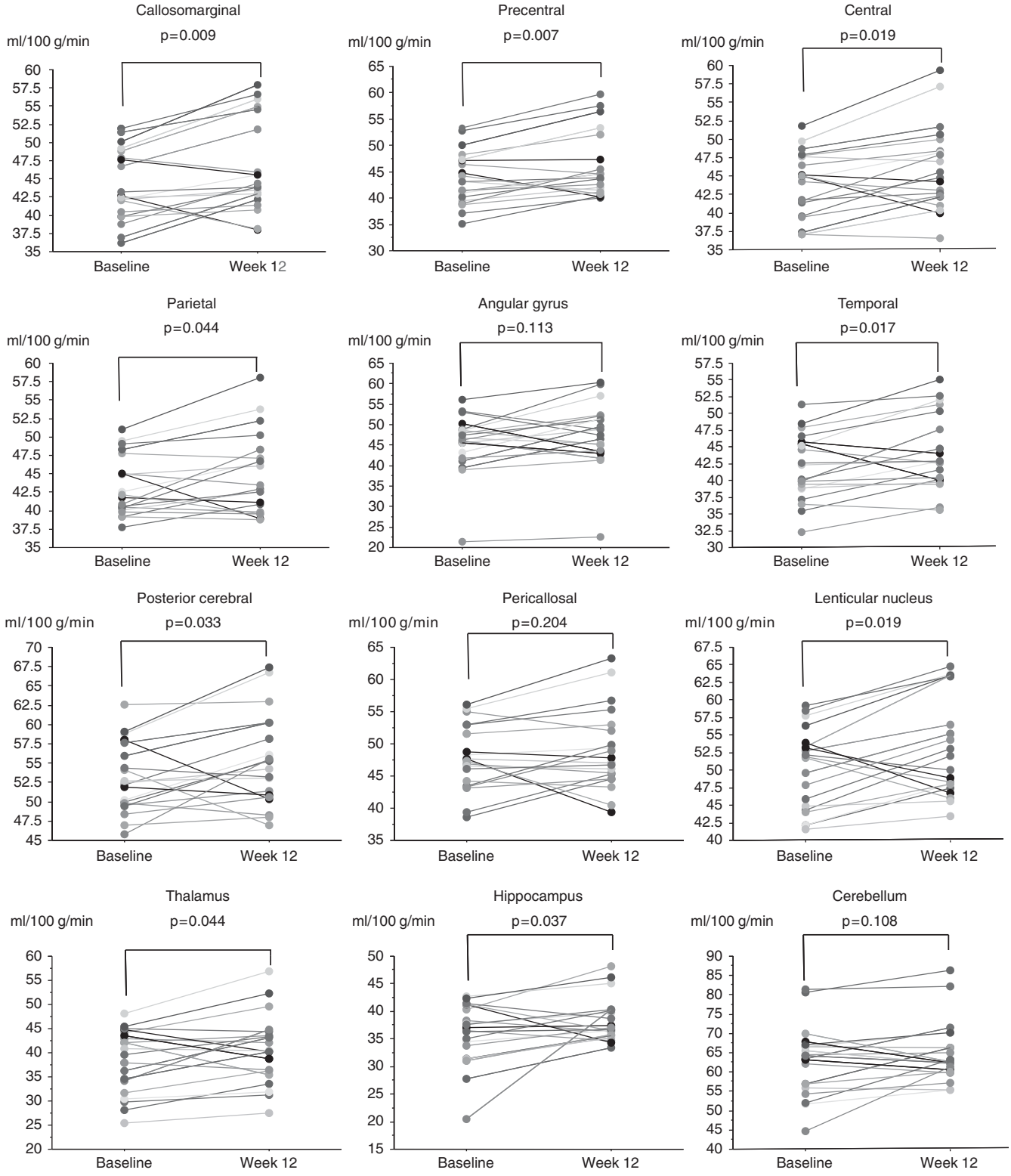

Figure 3 Change in regional CBF (rCBF) before and after telmisartan therapy. Significant increases in rCBF are observed in the callosomarginal, precentral, central, parietal, temporal, posterior cerebral, lenticular nucleus, thalamus, and hippocampus regions after 12 weeks of therapy. A full color version of this figure is available at the *Hypertension Research* journal online.

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