

Keywords:
arterial stiffness,
pulse wave
velocity,
angiotensin II
receptor blocker

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JRAAS 2001;2
(suppl 2):S8-S11

Effect of telmisartan on arterial distensibility and central blood pressure in patients with mild to moderate hypertension and Type 2 diabetes mellitus

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Abstract

Arterial wall stiffness is an important independent risk factor for cardiovascular disease in hypertensive patients, which is further exacerbated by co-existent diabetes mellitus. Increased arterial stiffness is directly associated with an increase in pulse wave velocity (PWV) and indirectly with increased central and peripheral blood pressure. Following a two-week placebo run-in period, 27 patients with mild to moderate essential hypertension and Type 2 diabetes mellitus, were randomised to once daily treatment with either telmisartan 40 mg or placebo for three weeks, and after a two-week washout period, crossed-over to the alternative treatment for a further three weeks. Carotid/femoral and carotid/radial PWV were measured non-invasively using the automatic Complior® device, and central parameters (central blood pressure, pulse contour analysis, and augmentation index) were measured using the SphygmoCor® system, at the start and end of each treatment period. Compared with placebo, treatment with telmisartan significantly reduced carotid/femoral PWV (mean adjusted treatment difference -0.95 m/s, 95% confidence intervals: -1.67, -0.23 m/s, $p=0.013$), as well as peripheral and central diastolic, systolic and pulse pressure. In conclusion, the results of this study show that telmisartan is effective in reducing arterial stiffness in hypertensive patients with Type 2 diabetes mellitus, and may potentially have beneficial effects on cardiovascular outcomes, beyond blood-pressure lowering effects, in this patient group.

Introduction

Hypertensive patients with either Type 1 or Type 2 diabetes mellitus are at increased risk of cardiovascular disease compared with age- and gender-matched controls.¹ Prospective clinical trials have demonstrated that intensive blood pressure (BP) control (to a target diastolic BP of between 80–85 mmHg) improves cardiovascular prognosis and results in an approximate halving of the cardiovascular risk.^{1,2} The object of lowering elevated BP is to avoid the development of arterial lesions and subsequent target organ damage, whether it be nephroangi sclerosis in the kidney, stroke in the brain, angina and myocardial infarction (MI) in the heart, or stenoses or aneurysms in the peripheral vasculature. In all of these conditions the arterial wall is the common denominator and the ultimate target at risk.

Arterial rigidity or stiffness increases with age and is an important independent risk factor for cardiovascular disease in hypertensive patients,^{3,4} and is correlated with the presence of atherosclerosis in

hypertensive patients.⁵ The extent of rigidity is further exacerbated in patients in whom hypertension and diabetes mellitus co-exist.⁶ Increased arterial stiffness is directly associated with an increase in pulse wave velocity (PWV) and indirectly with increased systolic and pulse pressures in both peripheral and central arteries.⁷ These effects are commonly observed in routine clinical practice, the clearest example being the elderly patient who may have a high systolic BP, a high pulse pressure and a low or normal diastolic BP (i.e., isolated systolic hypertension). The increase in pulse pressure over the increase in mean arterial pressure highlights the role of arterial changes and increased arterial stiffness in this pattern of haemodynamics.⁸ Pulse pressure is increased in patients with atherosclerosis and arterial diseases such as lower limb atherosclerosis and is also related to left ventricular hypertrophy (LVH) and other target organ damage such as intima medial thickening.⁹ An increased pulse pressure is an independent predictor of MI, congestive heart failure and cardiovascular death.⁷

In this study, we tested the hypothesis that telmisartan, a novel angiotensin II type 1 receptor antagonist (ARB), could significantly reduce PWV and central and peripheral BP in patients with essential hypertension and Type 2 diabetes mellitus. Pulse wave analysis, a validated non-invasive method,¹⁰ was used to assess indices of arterial wall stiffness.

Methods

This was a multicentre, randomised, prospective, double-blind, placebo-controlled crossover study in 27 patients with mild to moderate essential hypertension ($85 \text{ mmHg} \leq \text{diastolic BP} \leq 110 \text{ mmHg}$) and Type 2 diabetes mellitus. Patients with a systolic BP exceeding 180 mmHg were excluded. The study was conducted in accordance with the Declaration of Helsinki and all patients gave written informed consent prior to entry.

Following a washout period, patients completed a two-week placebo run-in period and were then randomised to once-daily treatment with telmisartan 40 mg or placebo for three weeks. At the end of this active treatment period, patients completed a second two-week placebo washout period and then crossed over to the alternative treatment for a further three weeks. Indices of arterial stiffness (see below) and central and peripheral BP were measured at entry to the study (week 0), at the end of each placebo run-in period (week 2 [baseline] and

**Journal of
the Renin-
Angiotensin-
Aldosterone
System**
(Including other
peptidergic systems)

September 2001
Volume 2
Supplement 2

Table 1 Patient characteristics.

Characteristic	Telmisartan/ placebo (n=13)	Placebo/ telmisartan (n=14)	All patients (n=27)
Age (years); mean (SD)	63 (7)	62 (12)	63 (10)
Male; n (%)	11 (85%)	8 (57%)	19 (70%)
Caucasian; n (%)	12 (92%)	9 (64%)	21 (78%)
BMI (kg/m ²); mean (SD)	27.9 (3.6)	28.7 (4.4)	28.3 (4.0)
Smoker or ex-smoker; n (%)	8 (62%)	3 (21%)	11 (41%)
Average alcohol consumption; n (%)	8 (62%)	2 (14%)	10 (37%)

SD = standard deviation; BMI = body mass index

Table 2 Treatment effects on carotid/femoral and carotid/radial pulse wave velocity (PWV, m/sec). Data are given as mean (SD) except where indicated otherwise.

	Telmisartan	Placebo
Carotid/femoral PWV		
N	20	20
Baseline	12.53 (2.50)	13.07 (1.84)
End of treatment	11.72 (2.30)	12.64 (2.15)
Change from baseline	-0.81 (1.48)	-0.44 (1.31)
Adjusted mean change from baseline (95% CI)	-1.10** (-1.60 to -0.60)	-0.15 (-0.65 to 0.36)
Carotid/radial PWV		
N	22	22
Baseline	10.35 (1.77)	10.83 (1.38)
End of treatment	9.72 (1.16)	10.49 (1.50)
Change from baseline	-0.62 (1.31)	-0.35 (1.56)
Adjusted mean change from baseline (95% CI)	-0.80 (-1.25 to -0.35)	-0.16 (-0.61 to 0.29)

Telmisartan vs. placebo **p<0.01

week 7), and at the end of each active treatment period (weeks 5 and 10). Patients were followed-up two weeks after the end of treatment.

Endpoints

The primary endpoint in the study was carotid/femoral PWV, which was assessed using the Complior® automatic device (Artech-Medical, Pantin, France), as previously reported.¹¹ This parameter was chosen as the main vessel along this vascular route is the aorta, an elastic artery, where atherosclerosis is focused. Secondary endpoints included the carotid/radial PWV, assessed using the Complior® automatic device, and central haemodynamic parameters (central BP, pulse contour analysis, and augmentation index), which were measured using the SphygmoCor® system.¹²

Measurement of PWV provides valuable information about arterial wall rigidity. Left ventricular contraction generates a pulse wave that propagates through the arterial wall, an elastic conduit. PWV is measured automatically as the ratio of the distance between proximal and distal probes to the time delay between registering proximal and distal pulse waves. This parameter has been previously shown to be a predictor of cardiovascular mortality and morbidity in hypertensive patients.⁴

Results

Of 27 patients included in the study, 13 patients were randomised to treatment with telmisartan followed by placebo, and 14 patients received placebo followed by telmisartan. With the exception of smoking history and alcohol consumption, which were more prevalent in the telmisartan/placebo group, the two groups were otherwise generally similar (Table 1).

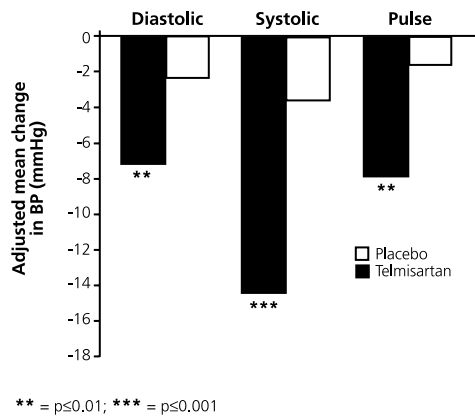
Treatment with telmisartan for three weeks produced a significant reduction in mean carotid/femoral PWV compared to three weeks of placebo (mean adjusted treatment difference -0.95 m/s (95% confidence intervals: -1.67 to -0.23 m/s, p=0.013). For differences in baseline measurements compared to telmisartan and placebo see Table 2. There was a less pronounced treatment effect on carotid/radial PWV (Table 2), probably reflecting the difference in physical characteristics between these two vessels; the aorta is relatively elastic, whereas the radial artery is more muscular and therefore treatment effects on arterial wall distensibility are less obvious. Treatment with telmisartan also produced significant decreases in peripheral and central systolic and diastolic pressures compared to placebo (Table 3). The observed reductions in peripheral and central pulse pressure with telmisartan were also significant (Figures 1 and 2).

Table 3 Treatment effects on peripheral and central blood pressure parameters (mmHg). Data are given as mean (SD) except where indicated otherwise.

	Telmisartan (n=23)		Placebo (n=23)	
	Systolic	Diastolic	Systolic	Diastolic
Peripheral blood pressure				
Baseline	147.6 (13.5)	89.8 (5.1)	149.9 (13.8)	89.7 (5.7)
End of treatment	134.9 (16.3)	82.8 (6.3)	145.6 (15.9)	87.0 (7.1)
Adjusted mean change from baseline (95% CI)	14.0*** (-18.2 to -9.9)	-7.0** (-9.2 to -4.8)	-3.0 (-7.1 to 1.2)	-2.7 (-4.9 to -0.5)
Central blood pressure				
Baseline	140.6 (15.2)	90.7 (6.7)	141.7 (16.2)	90.5 (6.3)
End of treatment	126.5 (17.8)	83.7 (5.7)	137.3 (16.5)	88.3 (7.1)
Adjusted mean change from baseline (95% CI)	-14.7*** (-18.8 to -10.7)	-6.9** (-9.1 to -4.6)	-3.7 (-7.8 to -0.4)	-2.4 (-4.6 to -0.2)

Telmisartan vs. placebo **p≤0.01; ***p≤0.001

Figure 1 Adjusted mean change from baseline (end of placebo run-in period) in peripheral blood pressure (mmHg) after treatment with telmisartan or placebo for three weeks.



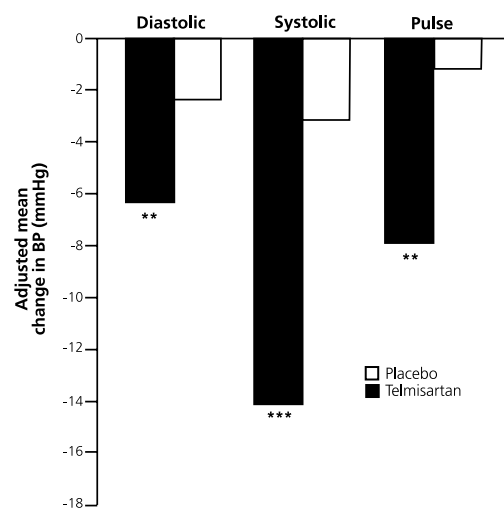
** = p≤0.01; *** = p≤0.001

The study was not designed to detect adverse events, due to small patient numbers, but there were few side effects with either treatment.

Discussion

The results of this study show that telmisartan is effective in reducing arterial stiffness, as measured by carotid/femoral PWV, as well as central and peripheral systolic, diastolic and pulse pressures in hypertensive patients with Type 2 diabetes. Although data are limited, the results of this study are consistent with other studies¹³ which have shown improvement in vascular compliance following treatment with other ARBs, as well as angiotensin converting enzyme inhibitors. Moreover, reports of persistence of improved compliance after withdrawal of such therapy suggest that these agents may produce long-term vascular remodelling.

Figure 2 Adjusted mean change from baseline (end of placebo run-in period) in central blood pressure (mmHg) after treatment with telmisartan or placebo for three weeks.



** = p≤0.01; *** = p≤0.001

In conclusion, the results of this study suggest that telmisartan may potentially have some influence on cardiovascular outcomes beyond the BP-lowering effect of treatment, which warrants further investigation in clinical studies.

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