Hypertension Research (2011) 34, 400–401

www.nature.com/hr

CORRESPONDENCE

Aliskiren reduces albuminuria and oxidative stress, and elevates glomerular filtration rates in Japanese patients with advanced diabetic nephropathy

Hypertension Research (2011) **34,** 400–401; doi:10.1038/hr.2010.250; published online 16 December 2010

Inhibition of renin angiotensin system is important in the treatment of diabetic nephropathy. At present, angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are being widely used clinically for this purpose. However, although these drugs decrease the urinary albumin excretion volume (urinary albumin-to-creatinine ratio: ACR), they also decrease the estimated glomerular filtration rate (eGFR). They also have the problem of increasing renin activity because of negative feedback.[1] Aliskiren, a direct renin blocker, was released in Japan in recent years, and the drug's safety and hypotensive effects have already been reported.[2,3] However, there are still few reports in Japan on the drug's effects on diabetic nephropathy. Although reports have already been released overseas on aliskiren's renal protection effects when used in combination with ACEIs and/or ARBs,[1,4] as well as its effects against eGFR,[5] there are very few such reports on Japanese patients. A basic study has shown aliskiren's potential to demonstrate renal oxidative stress suppression effects as well as renal protective actions by suppressing macrophage infiltration.[6,7] We therefore administered aliskiren to advanced diabetic nephropathy patients who were already taking ARBs and/or ACEIs, and observed the changes in ACR and eGFR. We also observed urinary oxidative stress (8-hydroxydeoxyguanosine: 8-OHdG), inflammatory chemokine (monocyte chemoattractant protein-1: MCP-1) and inflammatory cytokine (interleukin-6: IL-6) excretions.

We selected 31 individuals with stage III–IV diabetic nephropathy who were undergoing outpatient treatment at our hospital, administered 150 mg per day of aliskiren every other day for 2 months and evaluated the rate of change before and after administration of ACR, eGFR, urinary 8-OHdG, MCP-1 and IL-6. Regarding dosage and administration method, in view of the chief principle of drug administration, namely, of starting the dose at as low a level as possible, and aliskiren's long duration of activity (48 h),[8] we decided to observe the effects of the drug administered every other day for 2 months. The present study was conducted after obtaining informed consent from all subjects, and the study protocol was approved by the ethics committees of Tohoku University Hospital. Urinary 8-OHdG, MCP-1 and IL-6 were measured via enzyme-linked immunosorbent assay using, respectively, 8-OHdG ELISA kit (Japan Institute for the Control of Aging, Shizuoka, Japan), an MCP-1 ELISA kit (R&D Systems, Minneapolis, MN, USA) and an IL-6 ELISA kit (R&D Systems).

The results that showed a normal distribution was represented in terms of mean ± s.e.m., and those that did not were represented in terms of geometric mean (range). Student's *t*-test was used to compare and study the values of systolic blood pressure and eGFR before and after administration of the subjects who belonged to the former group, and the Wilcoxon signed rank test was used to compare and study ACR, 8-OHdG, MCP-1 and IL-6 for the latter-group subjects. $P<0.05$ was regarded as significant.

Clinical characteristics of the subjects at baseline are shown below. Age: 61.6 ± 2.4 (years), male/female: 13/18, diabetic duration: 12.6 ± 4.3 (years), systolic blood pressure: 145.2 ± 2.8 (mm Hg), glycated hemoglobin A1c: 6.5 ± 0.5 (%), ACR: 1320.5 (429.8–3427.9) and eGFR: 45.3 ± 2.2 (ml min^{-1}). The drugs taken by the subjects and their number were as follows. Antidiabetic agents: insulin 25, sulfonylurea (including glinides) 14, biguanide 15, α-glucosidase inhibitor 10, and pioglitazone 12. Antihypertensive agents: renin angiotensin system inhibitor: ARB monotherapy 14, ACEI monotherapy 4, and ARB+ACEI combination therapy 13. Calcium channel blocker: one kind 5, two kinds 8 and three kinds 18. Diuretics: thiazide 19, loop 12, spironolactone 9, α-blockers 5, β-blockers 9 and others 6.

Administration of aliskiren significantly decreased systolic blood pressure, ACR, 8-OHdG, MCP-1 and IL-6, and significantly increased eGFR (Table 1). The changes in systolic blood pressure, 8-OHdG, MCP-1, and IL-6 correlated positively to the changes in ACR ($y=2.0858x-12.388$, $r=0.47$; $y=0.9822x-9.1259$, $r=0.77$; $y=0.4489x-14.755$, $r=0.33$; and $y=0.5928x-8.0265$, $r=0.64$, respectively, with $P<0.001$ in all cases), but the changes in eGFR did not correlate to the changes in ACR ($y=0.0798x-26.696$, $r=0.04$, not significant.) Changes in the urinary 8-OHdG level at baseline correlated negatively to ACR's rate of change ($y=-4.4804x+15.1$, $r=0.41$, $P<0.001$).

Administration of aliskiren 150 mg every other day indicated its possible efficacy as treatment to suppress albuminuria and to improve eGRF in Japanese advanced diabetic nephropathy patients. The drug's ACR suppression effects were suggested to correlate to its actions of suppressing oxidative stress (8-OHdG) and tubulointerstitial damage (MCP-I and IL-6).[5–7] Moreover, the greater a patient's pretreatment oxidative stress, the greater were aliskiren's ACR suppressive effects,[9] so the increase in oxidative stress and inflammations caused by increased

Table 1 Changes in each parameter are evaluated before and after administration of aliskiren (150 mg per day, every other day, for 2 months) in 31 hypertensive subjects with advanced diabetic nephropathy

	Before	*After*	*% Change*
Urinary			
MCP-1 (pg mg^{-1} Cre)	503.3 (54.9–3144.0)	359.3 (38.8–2527.0)*	−24.1 ± 5.0
IL-6 (pg mg^{-1} Cre)	4.7 (0.2–36.5)	2.6 (0.2–18.5)*	−29.6 ± 7.3
8-OHdG (ng mg^{-1} Cre)	8.5 (4.3–17.5)	6.6 (4.4–14.8)*	−16.7 ± 5.2
ACR (μg mg^{-1} Cre)	1320.5 (429.8–3427.9)	841.6 (184.3–3783.1)*	−25.6 ± 6.7
SBP (mm Hg)	145.2 ± 2.8	135.8 ± 3.1*	−6.3 ± 1.5
eGFR (ml min^{-1})	45.3 ± 2.2	51.1 ± 2.5*	14.3 ± 3.4

Abbreviations: 8-OHdG, 8-hydroxydeoxyguanosine; ACR, urinary albumin to creatinine ratio; Cre, urinary creatinine excretion; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; SBP, systolic blood pressure.
*$P<0.05$, geometric mean (range), mean ± s.e.m.

renin activity may be closely related to the mechanism by which ACR increases in patients already undergoing treatment with renin angiotensin system inhibitors but who still see their nephropathy worsening.[10] The aliskiren's eGFR rise mechanism in this study is unknown. The eGFR rise action of aliskiren might be due to an increase of renal blood flow. However, renal blood flow is not measured in our study and a conclusion cannot be drawn.

The sample size of this study was too small for us to arrive at definitive conclusions; further investigation with a larger sample size is necessary. Furthermore, this study was not a randomized control trial (RCT) comparing aliskiren with controls. Further clinical research is necessary for clarifying these issues. This research is a preliminary investigation and definitely needs to be followed up with a large-scale RCT. A large-scale RCT of this type, designated as the Al pen-Glow (aliskiren prevents the estimated glomerular filtration rate decrease in Japanese hypertensive patients with chronic kidney disease) Study (UMIN000003678), is currently underway.

Susumu Ogawa[1,2], Kazuhiro Nako[1], Masashi Okamura[1,3], Miho Senda[1], Takefumi Mori[1] and Sadayoshi Ito[1]

[1]Division of Nephrology, Endocrinology and Vascular medicine, Tohoku University, Sendai, Japan; [2]Center for the Advancement of Higher Education, Tohoku University, Sendai, Japan and [3]Center for Translational and Advanced Research, Tohoku University, Sendai, Japan
E-mail: ogawa-s@mail.tains.tohoku.ac.jp

1 Düsing R, Sellers F. ACE inhibitors, angiotensin receptor blockers and direct renin inhibitors in combination: a review of their role after the ONTARGET trial. *Curr Med Res Opin* 2009; **25**: 2287–2301.
2 Kushiro T, Itakura H, Abo Y, Gotou H, Terao S, Keefe DL. Long-term safety, tolerability, and antihypertensive efficacy of aliskiren, an oral direct renin inhibitor, in Japanese patients with hypertension. *Hypertens Res* 2009; **32**: 169–175.
3 Ito S, Nakura N, Le Breton S, Keefe D. Efficacy and safety of aliskiren in Japanese hypertensive patients with renal dysfunction. *Hypertens Res* 2010; **33**: 62–66.
4 Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. AVOID Study Investigators: aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008; **358**: 2433–2446.
5 Splenser AE, Fisher ND, Danser AH, Hollenberg NK. Renal plasma flow: glomerular filtration rate relationships in man during direct renin inhibition with aliskiren. *J Am Soc Hypertens* 2009; **3**: 315–320.
6 Pilz B, Shagdarsuren E, Wellner M, Fiebeler A, Dechend R, Gratze P, Meiners S, Feldman DL, Webb RL, Garrelds IM, Jan Danser AH, Luft FC, Müller DN. Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension* 2005; **46**: 569–576.
7 Whaley-Connell A, Nistala R, Habibi J, Hayden MR, Schneider RI, Johnson MS, Tilmon R, Rehmer N, Ferrario CM, Sowers JR. Comparative effect of direct renin inhibition and AT1R blockade on glomerular filtration barrier injury in the transgenic Ren2 rat. *Am J Physiol Renal Physiol* 2010; **298**: F655–F661.
8 Chrysant SG. The antihypertensive effectiveness and safety of dual RAAS blockade with aliskiren and valsartan. *Drugs Today (Barc)* 2010; **46**: 151–162.
9 Ogawa S, Mori T, Nako K, Kato T, Takeuchi K, Ito S. Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. *Hypertension* 2006; **47**: 699–705.
10 Ogawa S, Kobori H, Ohashi N, Urushihara M, Nishiyama A, Mori T, Ishizuka T, Nako K, Ito S. Angiotensin II type 1 receptor blockers reduce urinary angiotensinogen excretion and the levels of urinary markers of oxidative stress and inflammation in patients with type 2 diabetic nephropathy. *Biomark Insights* 2009; **4**: 97–102.