CASE REPORT

Successful long-term effects of direct renin inhibitor aliskiren in a patient with atherosclerotic renovascular hypertension

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Received: 26 September 2016 / Accepted: 24 December 2016 / Published online: 16 January 2017
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Abstract A 64-year-old man visited our hospital with complaints of misty vision and ophthalmalgia. On admission, his blood pressure (BP) was high at 220/135 mmHg with no past history of hypertension, and he had choked discs. He was tentatively diagnosed as having idiopathic intracranial hypertension, and was later found to have atherosclerotic unilateral renovascular hypertension (RVH) based upon the extremely high plasma renin activity together with the radiological image tests. On day 3, combined antihypertensive therapies consisting of oral angiotensin II receptor blocker (ARB) and Ca channel blocker (CCB) along with intravenous CCB induced an abrupt BP lowering which led to deterioration of his renal function, progressing into acute kidney injury (AKI). Cessation of the ARB and reduction of the CCB dose ameliorated the AKI-related decline in renal function. On day 17, as he was reluctant to receive surgical intervention, he was treated with a direct renin inhibitor, aliskiren, combined with a half-dose CCB as a maintenance antihypertensive therapy. The therapy has proven not only successful to chronically maintain his renal function but was also capable of controlling his BP in the neighborhood of 130/85 mmHg over a period of 2 years. The present case suggests that the direct renin inhibition with aliskiren can be a safe and useful antihypertensive option to control hypertension and to preserve renal function in patients with atherosclerotic unilateral RVH.

Keywords Aliskiren · Direct renin inhibitor · Renovascular hypertension · Atherosclerosis · Renin angiotensin aldosterone system

Introduction

According to the survey conducted by the Ministry of Health, Labour and Welfare, approximately 30% of the adult population is estimated to have hypertension in Japan [1]. The majority of them are so-called essential hypertension of which the etiology is unknown. Among hypertensives with known etiology, renovascular hypertension (RVH) is a representative treatable type of hypertension accounting for 0.5–5% of overall hypertension [2–4]. The underlying causes of RVH are, in decreasing order, fibromuscular dysplasia (FMD), atherosclerosis, Takayasu arteritis and some other diseases such as the dissection of aorta or renal artery, and renal cell carcinoma. A recent trend of increasing number of the elderly may provoke a clinical caution on the diagnosis of age-related atherosclerotic RVH [5]. Namely, one must be careful when making a differential diagnosis of RVH in the aged patients, as there is always a possibility of coexisting essential hypertension, which normally increases by age. So, regardless of a potential indication of surgical intervention for RVH, the prescription of medications for RVH patients is still a cause for controversy for the majority of practitioners who deal with RVH.

The mechanism by which BP rises in RVH is explained by the activation of the renin-angiotensin-aldosterone system (RAAS) in the kidney due to renal ischemia originated from the narrowing of the renal artery [6]. The RAAS activation not only stimulates renin but also stimulates aldosterone, causing a mixture of renin-dependent and

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volume-dependent hypertension, at least, at a later stage of disease.

The treatments of RVH include surgical and non-surgical strategies. The most prevailing technology of the vasculo-surgical approach is percutaneous transluminal renal angioplasty (PTRA) which can be mainly indicated in younger subjects when the lesion is located in the main truncus of the renal artery. However, PTRA may not be considered for patients with atherosclerosis-based RVH. Indeed, recent studies have emphasized that PTRA is not advantageous or may be worse than antihypertensive medication especially in atherosclerotic RVH [7–9].

Although antihypertensive medication, per se, does not prevent progressive stenotic lesion in RVH, it may be beneficial not only to improve a patient's prognosis but to protect the contralateral kidney from failing. Selection of antihypertensives should include RAAS inhibitors such as ARBs or angiotensin-converting enzyme inhibitors (ACE-Is) (act by a renin-dependent mechanism) as well as agents with diuretic property (act by a volume-dependent mechanism) to secure stable BP reduction. Aliskiren is a new-class of orally active renin inhibitor which acts on renin directly [10]. The agent lowers BP by suppressing renin and consequently plasma renin concentration (PRC) in the two-kidney one-clip rats [11], animal model almost equivalent to unilateral RVH in humans. However, regardless of its theoretical benefit derived from pharmacological mode of action, aliskiren, in general, has not previously shown superior clinical outcomes; i.e., no trials to prove patient's prognosis, no superiority to other drugs, no firm add-on effect to another drug, and no clinical testing in hypertension with special conditions such as RVH or severely advanced hypertension. For these reasons, information regarding the clinical efficacy and safety of aliskiren in human RVH is very scant.

We herein report an elderly patient who developed unilateral RVH which has been successfully treated with aliskiren-based regime for a long period of time.

Case report

A 64-year-old man was found to be hypertensive for the first time on August at medical check-up. The patient had misty vision since the beginning of December. He was then referred to our hospital with complaints of misty vision and ophthalmalgia at the end of December. He has a past history of idiopathic thrombocytopenic purpura which had been asymptomatic for the past decades.

On examination, he was 162 cm, 65 kg, alert and communicative. He had a high BP of 220/135 mmHg, and choked discs. His serum creatinine (Cr) concentration was 1.00 mg/dL and estimated glomerular filtration rate (eGFR)

was 59 ml/min/1.73 m². Cerebrospinal fluid (CSF) examination showed CSF pressure of 38 cmH₂O (normal range is 6–18), cell count of 0.3 cells/mm³, protein concentration of 45 mg/dL and a glucose level of 74 mg/dL. Oligoclonal IgG bands were not detected in the CSF. Brain magnetic resonance imaging revealed only thickening of the optic nerve sheath. Tentatively, he was diagnosed as having idiopathic intracranial hypertension, and was admitted to the Division of Neurology emergently.

Commencement of antihypertensive therapies with intravenously-given CCB, nifedipine 2 mg/h (his body weight was 63.2 kg), orally-given CCB, amlodipine 10 mg/day, and the ARB, olmesartan 20 mg/day, led to a rapid decrease in BP below roughly 100–120/50–60 mmHg. This combined antihypertensive therapy was quite effective to improve his misty vision and ophthalmalgia. On day 3, however, this vigorous BP lowering resulted in a sudden increase in his serum Cr level from 1.00 (day 1) to 1.72 mg/dL (day 3), and the coincidental decrease in eGFR from 59 to 32 ml/min/1.73 m². He was then transferred to our Division of Nephrology and Hypertension under the diagnosis of acute kidney injury (AKI), which required further reno-protective treatments.

Laboratory data on admission to our division on day 3 is depicted in Table 1. The patient had thrombocytopenia, hypokalemia (3.1 mmol/L), elevated blood urea nitrogen (29 mg/dL), elevated serum Cr concentration (1.72 mg/dL), high plasma renin activity (PRA) level (63 ng/ml/h), and high plasma aldosterone concentration (PAC) level (135 pg/mL). Urinary electrolyte measurements showing depletion of Na and increased beta-2 microglobulin strongly suggested pre-renal type AKI.

An abdominal computed tomography (CT) scan revealed that the size of the right kidney was apparently smaller than that of the left (Fig. 1a). In addition, neither calcification nor a string of beads appearance in the branch of the renal arteries was found in the CT (Fig. 1b). A renal ultrasonography showed a proximal right renal artery stenosis along with a small-sized right kidney, which was accompanied by a lowered right renal blood flow on the power Doppler imaging (Fig. 2). The accurate peak systolic velocity at the stenosis, however, was not obtained because of technical difficulty. Peak systolic velocity was approximately 20.0 cm/s in the left segmental renal arteries and 12.0 cm/s in the right. In addition, right segmental renal arteries showed lack of early systolic peak unlike the left segmental renal arteries. Resistance index was approximately 0.6 in the both segmental arteries. ^{99m}Tc-mercaptoacetyl-triglycinerenography, which enables to evaluate effective renal plasma flow, showed that the uptake, T_{max}, and the excretion were delayed, revealing a markedly depressed renal function in the right kidney (Fig. 3). The final diagnosis of unilateral

Table 1 Laboratory date on day 3

Complete blood count	
WBC	10,700/ μ L
RBC	5.16×10^6 / μ L
Hb	13.9 g/dL
Ht	41.0%
Plt	120×10^3 / μ L
Endocrine test	
ACTH	32.7 pg/mL
Cortisol	15.3 μ g/dL
PAC	135 pg/mL
PRA	63.0 ng/ml/h
Adrenaline	35 pg/mL
Noradrenaline	395 pg/mL
Dopamine	21 pg/mL
Blood chemistry	
AST	13 U/L
ALT	10 U/L
LDH	233 U/L
ChE	332 U/L
T-Bil	0.5 mg/dL
ALP	198 U/L
γ GTP	21 U/L
TP	6.9 g/dL
Alb	3.5 g/dL
UN	29 mg/dL
Cr	1.72 mg/dL
eGFR	32 ml/min/1.73 m ²
UA	8.5 mg/dL
Na	137 mmol/L
K	3.5 mmol/L
Cl	97 mmol/L
BNP	5.9 pg/mL
Urine test	
U-protein	0.10 g/gCr
U-UN	637 mg/dL
U-Cr	124.3 mg/dL
U-Na	<10 mmol/L
U-K	15.2 mmol/L
U-Cl	<10 mmol/L
U- β_2 -MG	2069 μ g/gCr
U-NAG	4.7 U/gCr
U-Ald	95 μ g/day
U-MN	0.12 mg/day
U-NMN	0.33 mg/day

WBC white blood cell, RBC red blood cell, Hb hemoglobin, Ht hematocrit, Plt platelet, ACTH adrenocorticotrophic hormone, PAC plasma aldosterone concentration, PRA plasma renin activity, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ChE choline esterase, T-Bil totalbilirubin, ALP alkaline phosphatase, γ GTP: γ -glutamyltranspeptidase, TP total protein, Alb albumin, BUN blood urea nitrogen, Cr creatinine, eGFR estimated glomerular filtration rate, UA uric acid, Na sodium, K potassium, Cl chloride, BNP brain natriuretic peptide, UN urea nitrogen, β_2 -MG Beta-2 microglobulin, NAG N-acetyl-beta-D-glucosaminidase, Ald aldosterone, MN metanephrine, NMN normetanephrine

RVH was made with all this information together, namely the elevated RAAS components (on day 12, his PAC level was 370 pg/mL and PRA level was 27 ng/ml/h), the apparent smaller size of the right kidney by radiological images, and the reduced perfusion in the right renal artery obtained in the ^{99m}Tc-mercaptoacetyl-triglycine scintigraphy and the renal sonography.

In response to the occurrence of AKI (serum Cr concentration went up to 1.72 mg/dL), we immediately stopped the orally-given olmesartan and the intravenously-given nicardipine while the already-given amlodipine dose was decreased by half and this alteration maintained his BP in the neighborhood of 170/90 mmHg. His serum Cr level returned to the normal range within a few days. On day 15, we switched amlodipine 5 mg/day to long-acting nifedipine 60 mg/day for the purpose of having BP mildly decreased.

Treatment options for the future were given to the patient that covered both surgical interventions with PTRAs and medications. He was rather reluctant to receive PTRAs even after careful consideration on the benefit and the risk of PTRAs. Informed consent was then obtained from the patient. Accordingly, we decided on day 17 to add aliskiren initial dose of 75 mg/day on to the basally-dosed nifedipine 60 mg/day.

Figure 4 shows the fluctuation of his BP during the hospital stay and the following outpatient period. After discharge, we increased the dose of aliskiren gradually and finally to 300 mg/day, aiming at setting the target BP around 120–140/75–90 mmHg.

Figure 5 shows effect of treatment with aliskiren on PRA, PRC, PAC and urinary aldosterone levels. They were also kept within the acceptable range for a long time. Throughout this observation period, his serum Cr (Fig. 6) and potassium levels also remained within normal range, and no serious adverse events have been noted.

Discussion

The present case, relatively elderly, showed typical clinical manifestations compatible with unilateral RVH characterized by a sudden onset hypertension, activation of RAAS components (increased PRA and aldosterone), and typical radiological images. The patient unfortunately developed AKI due to iatrogenic abrupt decrease in BP. Knowing that patients with RVH normally respond well to RAAS blockers, we should have used the ARB more carefully as an initial treatment for RVH-based hypertensive emergency. Fortunately, aliskiren combined with CCB resulted in successful BP control in chronic treatment.

Fig. 1 Abdominal computed tomography images. **a** The size of the right kidney was smaller than that of the *left*. **b** Neither calcification nor a string of beads appearance was noted in the branch of the renal arteries. *Lt* left, *RA* renal artery, *Rt* right

Fig. 2 Renal artery stenosis detected by power Doppler imaging. Ultrasonography revealed proximal right renal artery stenosis (Indicated with an *arrow*). *Rt. RA* right renal artery

Diagnosing RVH with coexisting essential hypertension

One has to be cautious about making a diagnosis of RVH because the problem still remains unsolved as to the possibility of superimposed essential hypertension frequently found in the aged patients. The diagnosis of essential hypertension is to be made only after going through careful differential diagnosis of various type of hypertension. In other words, even if the patient was found to have RVH, it does not exclude coexisting essential hypertension. In this context, appropriate choice of antihypertensive medications, apart from surgical interventions, is crucial and must be an urgent need in the management of RVH.

Recent evaluation of surgical vs. non-surgical therapies in RVH

Recent studies including the ASTRAL trial [7], STAR study [8], and the CORAL trial [9], have shown that the application of PTRa for RVH might be rather problematic. Indeed, in the ASTRAL trial recruiting patients with atherosclerotic RVH, there was no evidence of clinical benefits of the PTRa-group compared to the medical-therapy group. To make matters worse, serious complications associated with PTRa occurred including death and amputations of limbs [7].

Antihypertensive therapies using RAAS blockers, ACE-Is or ARBs can inhibit aldosterone secretion, whereas PRA increases by way of the known feedback system. Unilateral renal artery stenosis in humans is compatible with the experimental animal model of “Two-kidney one-clip (2K1C) hypertension”. In the 2K1C model, PRA is secreted from the clipped ischemic kidney while the unclipped kidney stays hyperfiltrable [12]. Using ACE-Is or ARBs for this type could result in a rapid decrease in RAAS activity, promoting natriuresis, decreasing glomerular filtration rate, and secondarily, stimulating PRA. Careless use of ACE-Is or ARBs in this type may lead to AKI, similar to the one we have experienced here.

Direct renin inhibitor in the treatment of RVH

ARBs and ACE-Is are preferably chosen for anti-hypertensive therapy for unilateral RVH. Combination antihypertensive therapy with CCB and ARB could have presumably managed his BP after recovering AKI. However, CCB and ARB could not control all of the RAAS components because of the aforementioned changes in PRA.

Compared to ACE-Is or ARBs, the pharmacological action of direct renin inhibition with aliskiren is totally different, as it inhibits the upstream part of the RAAS axis,

Fig. 3 ^{99m}Tc -mercaptoacetyl-triglycine renography. The uptake, T_{max} and the excretion were delayed, revealing the markedly depressed renal function in the right kidney

Fig. 4 Effect of Aliskiren on blood pressure in a patient with RVH

theoretically enabling the inhibition of all RAAS components [10]. Aliskiren decreased not only PRA and PAC but also urinary aldosterone levels. Despite these unique pharmacological properties, clinical evaluation on aliskiren does not appear to be a cause for optimism. First of all,

aliskiren has not been accepted as a first line antihypertensive drug with substantial BP lowering potency such as other conventional drugs, like CCBs, ARBs, ACE-Is, diuretics and sympatholytic drugs. The main reason is that aliskiren has no clinical trials to prove better prognosis, no

Fig. 5 Treatment with Aliskiren on PRA, PAC, PRC, urinary aldosterone level. *PRA* plasma renin activity, *PAC* plasma aldosterone concentration, *PRC* plasma renin concentration, *U-Ald* urinary aldosterone level

superior BP lowering effect to other drugs, no firm add-on effect to another drug; moreover, there has been no clinical testing in hypertension with special conditions such as RVH or severe hypertension. What is worse is that the ALTITUDE trial showed that aliskiren added on to ACE-Is or ARBs increased the risk of non-fatal stroke, renal complications, hyperkalemia and hypotension in patients with diabetes mellitus [13]. Full dose of aliskiren (300 mg/day) added on to full dose of ACE-Is or ARBs therapy may worsen renal function in patients with decreased GFR in diabetes mellitus. All in all, clinicians think that because better-assessed antihypertensive drugs are already widely available, it would be better not to use aliskiren. To the best of our knowledge, there was no report so far on the clinical efficacy and safety of aliskiren in human RVH.

Aliskiren in CKD related hypertension

Regardless of the above-mentioned negative aspects of direct renin inhibition, aliskiren has potential clinical advantages. First of all, aliskiren is a long acting agent, exerting its effect for a longer period of time, which, for example, contributes to the augmentation of urinary sodium excretion more efficiently [14]. Second,

Moriyama et al. reported that aliskiren 150 mg/day, added on to ARB in patients with CKD reduced urinary protein and did not progress the renal dysfunction [15, 16]. Third, aliskiren increases renal plasma flow more than ACE-Is or ARBs do, and does not affect glomerular filtration rate, contributing to a protective effect in heart failure [17]. Finally, aliskiren could be used in lowering BP without serious side effects even in patients on dialysis [18]. These reports are suggestive that aliskiren may still be a potential option for the treatment of hypertension, not universally but with some forms of hypertension such as CKD and RVH.

We feel that it is too early to determine clinical indications for aliskiren in RVH, and to propose the appropriate dose. The ideal dose should be the one where maximum benefit of organ protective action can be attained, while having no serious adverse effects such as hyperkalemia, angioedema, thrombotic events and AKI. Meanwhile, the patient we described here has, at least, given us a hint that choosing aliskiren in patients with RVH deserves to be one of the treatment options. Further study will be required to determine to what extent direct renin inhibitor can be useful in protecting the kidney from damaging with a hope of improving patient's prognosis in RVH.

Fig. 6 Changes in creatinine and eGFR. eGFR: estimated glomerular filtration rate

Conclusion

Despite scarce information on using aliskiren in RVH, the present case suggests that this agent can be, at least, used to control BP in patients with atherosclerotic RVH.

Further study of direct renin inhibitors in patients with RVH warrants its appropriateness.

Acknowledgements A part of this case report was presented at the 4th Annual Scientific Forum of Clinical Hypertension of the Japanese Society of Hypertension held in Fukuoka, May 2015.

Compliance with ethical standards

Conflict of interest No conflict of interest is declared.

Informed consent Informed consent for using aliskiren and case reporting was obtained from the patient.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

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