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Aliskiren add-on therapy effectively reduces proteinuria in chronic kidney disease: An open-label prospective trial

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Abstract

Introduction: The combination therapy of aliskiren and renin–angiotensin–aldosterone system (RAAS) blocker in chronic kidney disease (CKD) is controversial. Whether such dual blockade can effectively apply to patients with CKD irrespective of stage and amount of proteinuria remains uncertain.

Methods: We added aliskiren at a dosage of 150 mg/day for six months in 103 Chinese CKD patients who had been treated with angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) and still had significant proteinuria or uncontrolled hypertension. Blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), potassium, and spot urine protein-to-creatinine ratio (UPCR) were measured at three and six months after aliskiren add-on therapy and compared with baseline.

Results: The combination of aliskiren and ACEi or ARB significantly reduced UPCR by 23% (p=0.001) and mean arterial pressure by 7.9 ± 13.8 mmHg (p<0.001) at six months. Twenty-five percent of subjects had a greater than 50% reduction in UPCR. No significant changes in eGFR and serum potassium level were noted at six months.

Conclusions: Adding aliskiren on ACEi or ARB in CKD patients, both in diabetes and non-diabetes, has a favorable effect on reducing residual proteinuria and inadequately controlled blood pressure.

Keywords

Aliskiren, proteinuria, chronic kidney disease

Introduction

The renin–angiotensin–aldosterone system (RAAS) cascade is an integral regulator of renal and cardiovascular structure and function, and accounts for many cardiovascular and renal abnormalities.[1] The inappropriate activation of RAAS plays a major role in the pathogenesis of cardiovascular and renal diseases. Therefore, in an attempt to interrupt the RAAS, the use of angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) emerges among the most popular renoprotective treatments in varying stages of chronic kidney disease (CKD) due to diabetes or non-diabetic kidney disease.

Aliskiren is recently introduced and has become the first oral drug to be proved for clinical use in hypertension in the class of direct renin inhibitor (DRI).[2] Similar to ACEi or ARB, aliskiren monotherapy can both effectively and safely reduce hypertension and proteinuria.[2,3] Moreover, a randomized, double-blind study suggested that aliskiren provides renoprotective effects by reducing proteinuria in patients of diabetic nephropathy with estimated glomerular filtration rate (eGFR) >30 ml/min per 1.73m^2 who have received the maximal dose of ARB.[4] Given the additional proteinuria lowering effects of dual RAAS blockade, and considering many patients with CKD still suffer from insufficient blood pressure control and proteinuria reduction, nephrologists show great interest in this aliskiren-based combination.[5] However, it remains in doubt whether such a strategy can safely and effectively apply to other forms of kidney disease besides diabetic nephropathy, as well as extend to advanced stages of

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CKD. Besides, another large-scale randomized controlled trial studying aliskiren-combined dual RAAS blockade therapy in high-risk patients with diabetes and renal impairment was halted recently due to the unexpected increased incidence of non-fatal stroke, hyperkalemia and hypotension.[6]

To clarify this question, the objective of the present study is to investigate the short-term efficacy of aliskiren on proteinuria as well as blood pressure reduction in CKD patients of various etiologies and stages who already receive a stable dose of ACEi or ARB.

Materials and methods

Patient selection

This is an open-label single-arm study performed in a single medical center, approved by an Institutional Review Board and Ethics Committee of Kaohsiung Chang Gung Memorial Hospital (99-3090B). The inclusion criteria were as follows: (1) adults aged > 18 years; (2) established diagnosis of CKD based on the presence of kidney damage or eGFR <60 ml/min per 1.73m^2 for more than three months, irrespective of etiology; (3) receiving a stable dose of ACEi or ARB for at least six months; (4) spot urine protein-to-creatinine ratio (UPCR) > 200 mg/g, and/or suboptimal blood pressure control with systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg. The exclusion criteria were: (1) concomitant use of both ACEi and ARB already; (2) if ever eGFR had dropped more than 30% within the first three months during any kind of RAAS blockade; (3) recent hospitalization within three months; (4) decompensated heart failure or liver cirrhosis; (5) transplant recipients; (6) dialysis patients; (7) unwilling to receive aliskiren or follow our treatment protocol.

Demographic data were recorded, including age, gender, body mass index (BMI), medications, associated diseases such as diabetes (identified by history, diagnosis barcode, current use of oral anti-diabetic agents, insulin injections or serum glycated hemoglobin > 6.5%), hypertension (identified by history, diagnosis barcode, systolic blood pressure over 130 mmHg and/or diastolic blood pressure over 80 mmHg for more than two out-patient-department visits, or concomitant use of antihypertensive agents), hyperlipidemia (identified by fasting serum total cholesterol or triglyceride above the upper limit of our laboratory definitions, >200 mg/dl and >150 mg/dl respectively, or concomitant use of statin or other lipid lowering agents) and hyperuricemia (identified by history, diagnosis barcode, current use of allopurinol or uricosuric agents, or serum uric acid above the upper limit of our laboratory definition, >8.3 mg/dl). Their renal function, eGFR, was calculated by equation derived from the Modification of Diet in Renal Disease (MDRD) study.

Laboratory methods

To evaluate proteinuria status we adopted spot urine sample for its convenience and reliability as a precise indicator of 24-hour proteinuria, according to the National Kidney Foundation.[7] Urine total protein was measured by colorimetric assay, using Pyrogallol red as dye-binding (Wako Diagnostics and Chemicals USA Inc.). Urine creatinine was measured by colorimetric assay using MeDiPRO creatinine kinase test.[8]

Treatment protocol and follow-up

All eligible subjects were treated with aliskiren at a dose of 150 mg/day for six months.

At each clinic visit at baseline (screening and patient selection) and three and six months after starting aliskiren, systolic, diastolic and mean arterial pressure (MAP, calculated as 1/3 systolic pressure + 2/3 diastolic pressure) were measured; serum creatinine, potassium and spot UPCR were determined. During the study period, all antihypertensive agents, including ACEi or ARB, were continued and maintained at the prior dosage. All adverse events such as stroke, cardiovascular event and acute renal shutdown during the study period were recorded.

End points

The study was designed to evaluate the antiproteinuric effects of aliskiren-add-on therapy in CKD patients with residual proteinuria or suboptimal blood pressure control in spite of ongoing ACEi or ARB use. The primary end point was change in amount of proteinuria. Secondary end points were change in blood pressure, renal function as evaluated with eGFR, and serum potassium level. Factors that might affect the therapeutic response, including change in proteinuria, MAP and eGFR, were analyzed.

Statistical analysis

To establish an appropriate sample size, we referred to the results of the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study, which disclosed 18% UPCR reduction in type 2 diabetic subjects after six months of aliskiren add-on therapy. Taking into account our inclusion of participants with a more advanced CKD stage, heavier proteinuria and more heterogeneous renal disease entities, we underrated the UPCR reduction effect to 10%, assuming a standard deviation (SD) of 30%. To reach a 90% power at a significance level of 0.05 using a two-sided one-sample *t*-test, a target sample size would be 97. Finally we recruited 103 subjects.

The study sample characteristics were summarized using descriptive statistics with categorical data as counts with percentages and continuous data as mean with SD.

UPCR is log-transformed during calculation and expressed as geometric mean as not normally distributed. All serial data were compared by means of a general linear model for repeated measures, followed by a generalized estimating equation. Univariate analysis was performed using simple linear regression for categorical and continuous variable. The same factors were included in the multivariate analysis using multiple linear regression. UPCR reduction rate and eGFR decline rate were dependent variables and age, gender, BMI, diabetes, hypertension, hyperuricemia, hyperlipidemia, the magnitude of baseline eGFR, baseline MAP, baseline UPCR and change in MAP from baseline to six months were selected as independent variables. A p-value < 0.05 is considered statistically significant. By using multiple linear regression for repeated measures, we interpreted the generalized estimating equation to adjust MAP and calculate the predicted mean and confidence interval for UPCR at baseline and three and six months. Statistical analyses were performed with the R Project for Statistical Computing, version 2.12.0. for Windows.

Results

Demographic data

Table 1 lists the demographic characteristics of a total of 103 Chinese participants. Males accounted for 53% of study subjects; their mean age was 63.4 ± 13.0 years; mean eGFR was 37.4 ± 24.4 ml/min per 1.73m^2. The proportion of CKD from stage 1 to 5 was 5%, 10%, 40%, 25% and 20% respectively. Baseline UPCR was 896 mg/g (95% confidence interval, 701–1046 mg/g). Among enrolled patients, 91% had hypertension, 41% had diabetes, 43% had hyperuricemia and 62% had hyperlipidemia. As for underlying renal disease, 41% of enrolled patients had diabetic kidney disease, 15.5% had biopsy proven chronic glomerulonephritis, one had solitary kidney and others had unproven etiologies for kidney disease. Of all patients, 30% used aliskiren plus ACEi or ARB as the only two antihypertensive agents, 36% needed three and 34% used more than three agents.

Table 1. Demographic data of 103 participants.

Age, years (mean ± standard deviation)	63.4 ± 13.0
Gender, male (%)	53.0
Body mass index (kg/m^2)	26.3 ± 3.6
Hypertension (%)	91.0
Diabetes (%)	40.8
Hyperuricemia (%)	43.0
Hyperlipidemia (%)	62.0
Serum creatinine (mg/dl)	2.3 ± 1.4
eGFR (ml/min per 1.73 m^2)	37.4 ± 24.4
UPCR (mg/g)	1106.9 ± 1819.1
Systolic blood pressure (mmHg)	144.4 ± 19.4
Diastolic blood pressure (mmHg)	76.1 ± 10.8
Serum potassium level (mmol/l)	4.7 ± 0.6
CKD stage 1 (%)	5
CKD stage 2 (%)	10
CKD stage 3 (%)	40
CKD stage 4 (%)	25
CKD stage 5 (%)	20
Aliskiren + ACEi (%)	5.0
Aliskiren + ARB (%)	95.0
Two antihypertensive agents used (aliskiren + ACEi or ARB) (%)	30.0
Three antihypertensive agents used (%)	36.0
≥ 4 antihypertensive agents used (%)	34.0

eGFR: estimated glomerular filtration rate; UPCR: urine total protein-to-creatinine ratio; CKD: chronic kidney disease; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Primary and secondary outcomes

At three months, the mean UPCR declined to 835 mg/g (583–1196 mg/g), a 7% reduction; by the end of the six-month study period, UPCR was further reduced to 689 mg/g (529–897 mg/g), a 23% reduction from baseline (p=0.001, Table 2). Besides, one quarter of patients (32 subjects) had a greater than 50% reduction in UPCR at six months; among them, 18 patients were CKD stage 3 (eGFR 30–60 ml/min per 1.73m^2), 13 patients belonged to baseline UPCR less than 1000 mg/g, 16 patients to UPCR 1000–3000 mg/g and three to greater than 3000 mg/g.

When allocating patients according to baseline proteinuria, patients with UPCR 1000–3000 mg/g at baseline (N=38) had UPCR reduction from 1673 mg/g (1522–1838 mg/g) to 1131 mg/g (873–1465 mg/g), a 32% reduction (p=0.002, Figure 1). Subjects with UPCR<1000 mg/g at baseline (N=50) had a trend of UPCR reduction from 326 mg/g (251–423 mg/g) to 270 mg/g (203–361 mg/g) in six months; those with UPCR>3000 mg/g at baseline (N=15) had a trend of UPCR decline from 5381 mg/g (4166–6950 mg/g) to 4449 mg/g (2991–6619 mg/g) at the end of the study.

When subdividing participants by the status of diabetes, the diabetic group had significant UPCR reduction from 985 mg/g (696–1393 mg/g) at baseline to 879 mg/g (561–1379 mg/g) at three months, and to 785 mg/g (452–1365 mg/g) at six months (p=0.031, Figure 2). For non-diabetic patients, UPCR was decreased from 615 mg/g (463–817 mg/g) at baseline to 527 mg/g (360–772 mg/g) at three months, and 452 mg/g (279–730 mg/g) after six months of add-on therapy (p=0.002, Figure 2).

The mean eGFR at three and six months was 35.0 ± 24.2 and 32.8 ± 19.9 ml/min per 1.73m^2 and there was no significant change compared with baseline (p=0.708, Table 2). When dividing patients according to baseline eGFR, all subgroups had unremarkable change throughout the study period (Figure 3). For patients with UPCR<1000 mg/g and >3000 mg/g at baseline, no significant change of eGFR was

Table 2. Changes in UPCR, eGFR, systolic, diastolic, mean arterial pressure and serum potassium level during six-month study period.

	Baseline	Three months	Six months	*p* value
UPCR, mg/g (geometric mean (95% confidence interval))	896 (701–1046)	835 (583–1196)	689 (529–897)	0.001
eGFR, ml/min per 1.73 m^2 (mean ± standard deviation)	37.4 ± 24.4	35.0 ± 24.2	32.8 ± 19.9	0.708
Systolic blood pressure, mmHg	144.4 ± 19.4	135.7 ± 16.1	131.2 ± 16.2	<0.001
Diastolic blood pressure, mmHg	76.1 ± 10.8	73.6 ± 10.7	70.7 ± 10.5	<0.001
Mean arterial pressure, mmHg	98.9 ± 12.9	94.3 ± 11.5	90.9 ± 11.3	<0.001
Serum potassium, mmol/l	4.7 ± 0.6	4.6 ± 0.6	4.7 ± 0.6	0.314

UPCR: urine total protein-to-creatinine ratio; eGFR: estimated glomerular filtration rate.

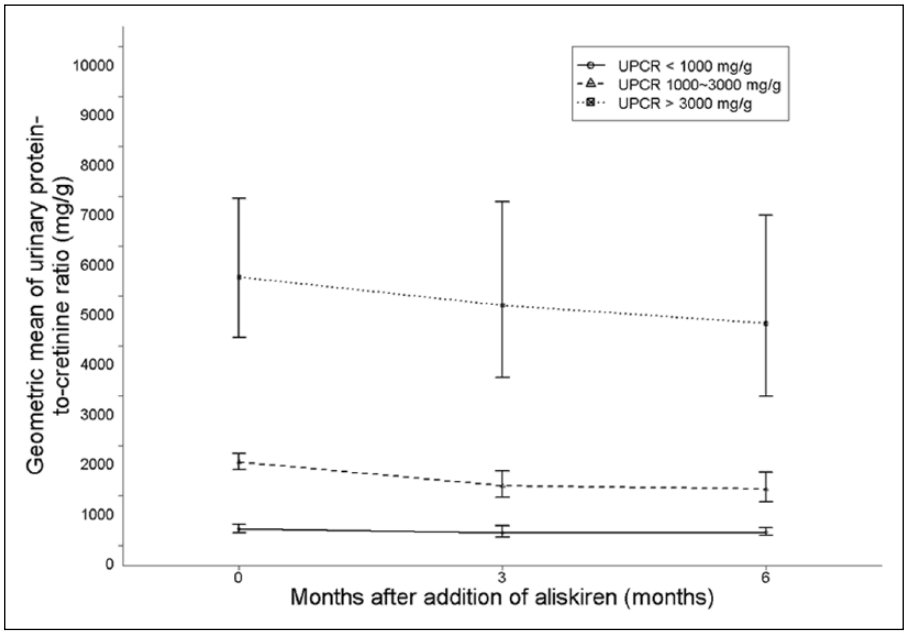

Figure 1. Changes in urinary protein-to-creatinine ratio (UPCR, geometric mean values with 95% confidence intervals) in subgroups of different baseline proteinuria status.

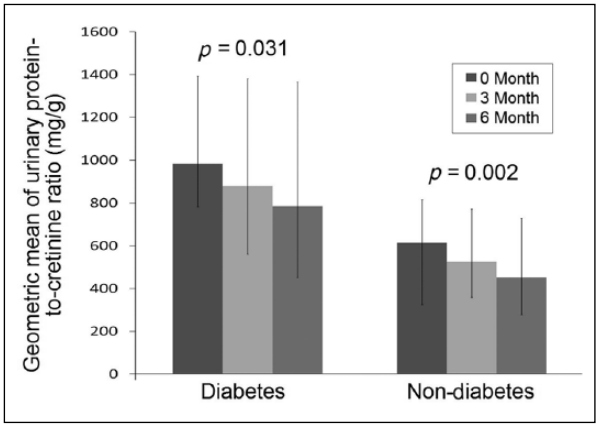

Figure 2. Changes in urinary protein-to-creatinine ratio (UPCR, geometric mean values with 95% confidence intervals) in diabetics and non-diabetics.

noted; while in those with UPCR 1000–3000 mg/g, a modest but significant decline (from 35.5 to 31.2 ml/min per 1.73m^2, p=0.031) was found.

MAP was reduced by 4.3 ± 13.2 mmHg at three months (4.4 ± 13.3 mmHg in diabetic group, 4.3 ± 13.3 mmHg in non-diabetic group) and 7.9 ± 13.8 mmHg at six months (6.7 ± 15.1 mmHg in diabetic group, 8.7 ± 12.8 mmHg in non-diabetic group) by aliskiren add-on therapy (p<0.001). No significant difference existed between diabetic and non-diabetic group. There was no change in other antihypertensive medications throughout the study period.

Adverse events

No participant was withdrawn during the six-month study period due to intolerable adverse events. Four subjects experienced an eGFR decline of over 30% at the end of the study,

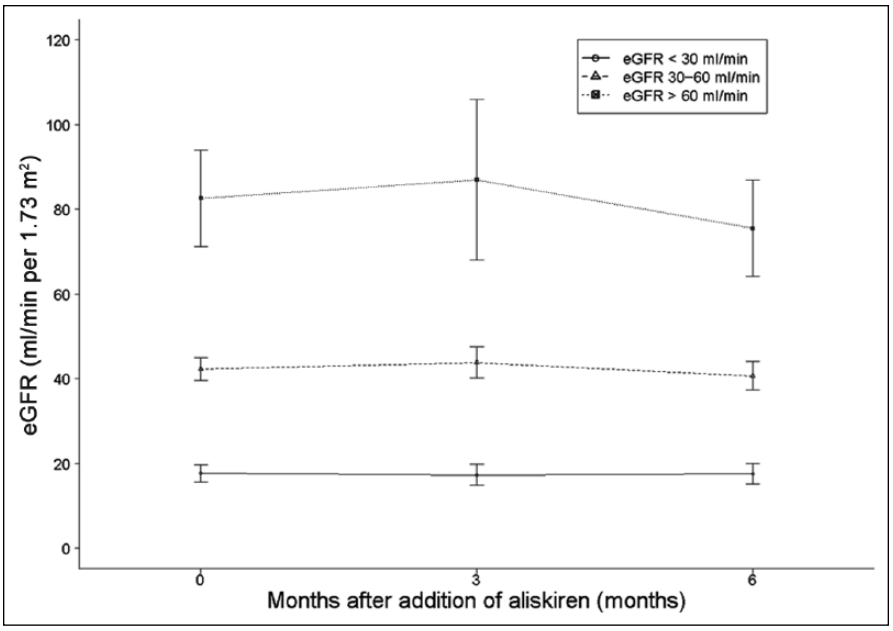

Figure 3. Changes in estimated glomerular filtration rate (eGFR) (mean ± standard deviation) in subgroups of different baseline eGFR.

while an increase of over 30% was noted in four patients. Serum potassium level showed an insignificant change during the study period at three and six months ($p = 0.314$, Table 2). Three subjects developed hyperkalemia at three months, and one of them had the highest potassium level: 6.5 mmol/l. At six months, hyperkalemia was noted in seven patients and three of them had serum potassium 6–6.5 mmol/l. All were in CKD stage 4 or 5, were asymptomatic and continued their medications, adding polystyrene sulfonate and diet education to normalize serum potassium. There was no report of symptomatic hypotension, stroke, death, acute coronary syndrome or events that led to hospitalization from the start of study to the present. The headache, dizziness or nasopharyngitis reported infrequently in previous studies were hardly found in our patients.

Factors that may affect therapeutic response

Both univariate and multivariate analysis showed that neither the UPCR reduction rate nor the eGFR decline rate during treatment was affected by age, sex, BMI, diabetes, hypertension, hyperuricemia, hyperlipidemia, the magnitude of basal eGFR, basal MAP, basal UPCR or change in MAP from baseline to six months. After adjustment for MAP change, UPCR reduction remains unaffected and remarkable (p=0.02).

Discussion

In the present study, we show a favorable effect of the combination of aliskiren and ACEi or ARB on residual proteinuria and blood pressure reduction irrespective of CKD stage and kidney damage etiology, after patients have been treated by ACEi or ARB for more than six months. Six months of aliskiren add-on reduced UPCR by 23%; one-quarter of subjects had more than 50% reduction. Also, MAP was reduced by 8 mmHg at six months. It suggests that the therapeutic response to aliskiren add-on in CKD is not confined to diabetic nephropathy and occurs regardless of the magnitude of proteinuria and renal function. There was a non-significant decline in eGFR or increase in serum potassium level throughout the study period, while infrequent incidences of hyperkalemia in advanced CKD stage merit clinicians' surveillance.

Since the disclosure of success in treatment of early stage diabetic nephropathy from the AVOID study,[4] several investigators extended aliskiren add-on therapy to other forms of kidney damage, including immunoglobulin A nephropathy, primary membranous glomerulopathy and non-diabetic nephropathy.[4,9–13] The study designs differed, being either a double blind, randomized, controlled trial like the AVOID study, or a single-arm study like ours.[9–11] The dosage of aliskiren in trials ranges from 150 mg to 300 mg per day. The proteinuria reduction rate was around 20% in six months by either dosage[4,10,13] and Gupta et al. reported up to 75.9% reduction in nine patients of primary membranous glomerulopathy achieved with 300mg per day for three months.[11] However, these studies were limited to early stage nephropathy with mild to moderate proteinuria. Our study included patients across varying stages of CKD and also those with heavy proteinuria.

Our study confirms the antihypertensive effect of aliskiren as the second RAAS blockade agent and shows a

further reduction of 8 mmHg at six months. Previous studies also demonstrated that by combining aliskiren with either ramipril or valsartan provided a further reduction in blood pressure than either drug alone (2.7/1.2 mmHg reduction in systolic/diastolic pressure at 26 weeks, and 4.4/2.5 mmHg at eight weeks, respectively).[14,15] On the contrary, the AVOID study revealed an insignificant reduction in blood pressure compared with baseline or placebo group. This discrepancy possibly results from different inclusion criteria and study design: we enrolled subjects with suboptimal blood pressure control while the AVOID study used the maximal recommended dose of losartan (100 mg daily) with additional antihypertensive therapy to achieve blood pressure <130/80 mmHg before initiation of aliskiren.[4]

In spite of the appreciable blood pressure lowering effect, the antiproteinuric effect conferred by aliskiren add-on is still significant and independent of changes in blood pressure, as indicated by both univariate and multivariate analysis. Dual RAAS blockade has been shown to offer better blood pressure control as well as proteinuria reduction, and provides a promising result in advanced proteinuric nephropathy.[16] The 23% reduction in UPCR at six months and more than half reduction in one-quarter of subjects are comparable to the AVOID study results.[4]

Indeed, residual proteinuria has been historically viewed as a driving force in ongoing renal function loss, and reducing residual proteinuria is renoprotective. Both the post-hoc analyses of REIN and RENAAL studies indicate that the proteinuria reduction after three months of ramipril or albuminuria reduction after six months of losartan reliably predict long-term disease progression.[17,18] Therefore, the inhibition of renin from the upstream theoretically offers more renoprotection by minimizing the hazardous residual proteinuria, as our study showed. Recently some Japanese groups found that addition of aliskiren to ARB ameliorates tubular injury and oxidative stress in both diabetic and non-diabetic nephropathy.[9,12,19] Cherney et al. also noticed that aliskiren-based dual RAAS blockade was associated with greater arterial compliance, flow-mediated vasodilatation and renal vasodilatation in type 1 diabetic patients.[20] Furthermore, improvement in glucose homeostasis and glomerular filtration rate along with several renal variables in diabetic rats has been reported to be achieved by combining aliskiren and olmesartan.[21] All of these studies open a new insight into the role of RAAS in the pathogenesis of CKD and therapeutic benefits derived from DRI administration.

On 20 December 2011, Novartis announced termination of the ALTITUDE trial studying aliskiren on top of ACEi or ARB therapy in high-risk patients with type 2 diabetes and renal impairment.[6] The Data Monitoring Committee noticed an increased incidence after 18–24 months of non-fatal stroke, renal complications, hyperkalemia and hypotension, which are all unremarkable in our preliminary results. The ALTITUDE study enrolled subjects with a history of cardiovascular disease.[22] We excluded those with a history of eGFR drop of more than 30% within the first three months of RAAS blockade therapy, which follows The National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guideline.[23] Lastly, over-suppression of blood pressure might be the culprit, as virtually all patients in ALTITUDE had already-treated hypertension, with a median systolic/diastolic blood pressure of 134.7/74.3 mmHg; 10/2 mmHg lower than our cohort.[22] Likewise, our results contrast with the ONTARGET study, which combined ramipril and telmisartan in patients aged 55 years or older with established atherosclerotic vascular disease, among whom only 13.1% had microalbuminuria and 4% had macroalbuminuria.[24] Dual RAAS blockade might not confer additional renoprotection over monotherapy in patients with hypertension, diabetes or increased cardiovascular risk without proteinuria, but does have great potential in advanced renal patients.[16,25]

Our limitations include short follow-up duration of six months, no placebo control arm, not a double blind trial, and relatively small number of examinees. A single-arm study with open-label might be an improper setting to confirm the safety of aliskiren add-on therapy. However, through this pilot study, we attempt to alert clinicians to the importance of patient selection in applying dual RAAS blockade, instead of declining their remarkable and beneficial impacts on proteinuria and blood pressure reductions in the CKD cohort.

Conclusions

The combination of aliskiren on top of ACEi or ARB in CKD patients has a significant and favorable effect on reducing residual proteinuria and inadequately controlled blood pressure, without compromising renal function. The therapeutic response is not limited to diabetic nephropathy, and can be extended to heterogeneous forms of nephropathy in various stages of renal function and proteinuria. The side effects of add-on therapy seem minor and tolerable in our study.

Conflict of interest

None declared.

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