Effect of Direct Renin Inhibitor Monotherapy on Proteinuria in Overt Diabetic Nephropathy

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Background: *Diabetic nephropathy is one of the major causes of chronic kidney disease (CKD), consequently progression to end stage renal disease. The previous studies demonstrated that the inhibition on renin-angiotensin-aldosterone system (RAAS) such as by angiotensin converting enzyme inhibitor (ACEI) and angiotensin type I receptor blocker (ARB) reduced proteinuria and slow progression of CKD. Direct renin inhibitor (DRI) theoretical complete block RAAS by reducing plama renin activity, angiotensin I and angiotensin II. The present study aimed to determine the efficacy of aliskiren (DRI) monotherapy on blood pressure control and proteinuria reduction.*

Material and Method: *Diabetic mellitus patients with estimated glomerular filtration rate (eGFR) $\geq$ 30 ml/min who had proteinuria > 300 mg/day were enrolled to receive aliskiren 150 mg/day for 2 weeks then 300 mg/day until 24 weeks.*

Results: *The SBP were significantly decreased form 137.8 to 123.7 (p = 0.01) at 2 weeks, 137.8 to 126.26 (p = 0.04) at 4 weeks and 137.8 to 121 mmHg (p = 0.002) at 24 weeks after treatment, respectively. Similar to SBP, the DBP was significantly decreased from 84.08 to 73.66 (p = 0.04) at 4 weeks and 84.08 to 75.85 mmHg (p = 0.002) at the end of study. Reduction of UPCR showed significantly reduced for 32.65% (p = 0.007) and 45% (p = 0.004) from baseline at 2 weeks and 24 weeks after DRI treatment respectively. Serum creatinine, eGFR and serum potassium were no significant changed from the baseline. There were no harmful adverse reaction in patients who receiving aliskirin.*

Conclusion: *Aliskiren monotherapy showed significantly reduced proteinuria, good blood pressure control without harmful side effect in overt diabetic nephropathy patients.*

Keywords: *Direct rennin inhibitor, RAAS system, Diabetic nephropathy, Proteinurea*

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Diabetic nephropathy (DN) is a leading cause of end-stage renal disease throughout much of the world accounting for more than one-third of new cases in the United State of America[1]. A survey in Thailand found that patients with type 2 Diabetes mellitus (DM) have DN was 42.9% prevalence, 19.7% for microalbuminuria and 23.2% for overt nephropathy[2]. According to these evidences, DN is the major health problem in Thailand and worldwide. The pathophysiology of diabetic nephropathy involving in hemodynamic stress in concert with metabolic pathways that are activated by hyperglycemia, glycated proteins and oxidative stress induce a host of growth factors in the kidney. The fibrogenic cytokine transforming growth factor-beta (TGF-β) is the etiologic agent of renal hypertrophy and the accumulation of mesangial extracellular matrix components in DN[3,4]. There is a link between the renal manifestations of DM and renin angiotensin aldosterone system (RAAS). Angiotensin II in turn stimulates the podocyte to produce collagen protein, a constituent of the glomerular basement membrane (GBM). Alterations in the production of the novel chains of collagen may contribute to the altered properties of the GBM such as thickening and perhaps the proteinuria of DM, the earliest clinical evidence of diabetic nephropathy. This pathway eventually leading to glomerulosclerosis including interstitial fibrosis resulting in deterioration of the kidney function[3,5-7].

The RAAS inhibition in both animals and patients with diabetic kidney disease from drug use angiotensin coverting enzyme inhibitor (ACEI)[5] or

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angiotensin type I receptor blocker (ARB)[8-10] and combination treatment of ACEI and ARB[11] can prevent and delay deterioration of kidney function. Current treatment, aimed at slowing progression of disease, centers on two inter-related therapeutic strategies: blood pressure reduction and blockade of the RAAS[12-14]. Such treatments have been shown to reduce the functional changes seen in DN and also to attenuate the structural abnormalities that characterize this disease[15]. Attempts to maximize the effectiveness of this strategy have led to the use of ACE inhibitor and ARB combinations[16] as well as supra-maximal and ultra-high doses of single agents[17].

More recently, direct renin inhibition (DRI) has also emerged as a potential therapeutic strategy to block the RAAS and lower blood pressure[10]. Aliskiren, the first in a new class of orally effective DRI, differs from ACEI and ARB in its ability to lower plasma renin activity (PRA), there by inhibiting the production of both angiotensin I (Ang I) and angiotensin II (Ang II)[18]. In previous study, the combination treatment with aliskiren and ACEI[18] and aliskiren and ARB[19] proved the effectiveness in proteinuria and blood pressure reduction. However, it is not known whether such treatment in diabetic patients leads to blood pressure lowering and proteinuria reduction using DRI alone. Accordingly, in the present study the authors sought to determine the effectiveness, toralibility of DRI in DN as monotherapy.

Material and Method

Study design

This prospective, opened label, study was done in the Thammasat Chalermprakiat hospital between October 2009 and September 2010. The study protocol was in accordance with the Declaration of Helsinki (2008) and was approved by research ethics committee, faculty of medicine, Thammasat University. All patients provided written informed consent.

The authors enrolled patients who are at least 18 years of age, type 2 DM with 24 hr urine protein more than 300 mg or urine protein creatinine ratio (UPCR) more than 0.3 and systolic blood pressure (SBP) and diastolic blood pressure (DBP) more than 130/80 mmHg. The criteria for exclusion were known nondiabetic kidney disease, estimated glomerular filtration rate (eGFR) less than 30 ml/min, chronic urinary tract infection, a serum potassium level more than 5.1 mmol/l, major cardiovascular disease within the previous 6 months and female who are breast feeding, pregnant or plan to become pregnant or cannot comply with contraceptive methods by the researchers suggestion. All patients must not previously received ACEI, ARB or DRI at least 6 months.

Baseline data including patient weight and height, blood pressure, serum creatinine (SCr), eGFR, CBC, electrolyte, urine analysis, 24 hr urine for protein, UPCR, and the presence of comorbidities were collected at entrollment. Estimated glomerular filtration rate (eGFR) was calculated from the standard Cockcroft-Gault equation. All patients received aliskiren 150 mg/day for the first 2 weeks then 300 mg/day until 24 weeks. Blood pressure, SCr, serum electrolyte, UPCR, adverse events and adherence to medication were assessed at 2, 4, 12 and 24 weeks. All patients were continued to receive their usual care for diabetes and hypertension at OPD follow-up.

The primary outcome was the percentage reduction in the UPCR from baseline at 24 weeks. Secondary endpoints included relative changes in SCr and eGFR, serum potassium, blood pressure and adverse reactions.

Statistic analysis

Continuous data such as ages, weight, height, SCr, eGFR, serum potassium, UPCR, blood pressure, was analyzed by the Student's t-test for equal variance or Mann-Whitney test for unequal variance. The categorical variables such sex, was investigated by Pearson χ^2 or Fisher's exact test. A two-sided p-value ≤ 0.05 was considered significant. Results are expressed as mean $\pm$ SD unless indicated otherwise.

Results

Fifteen patients were enrolled to the present study. A 11 of 15 (73.3%) patients were male and 4 of 15 (26.7%) patients were female. An average of age were 57.2 ± 11.0, 55.8 ± 7.8 and 61.25 ± 7.4 years for all, male and female patient, respectively. Mean of SBP and DBP were 137 ± 17.6 and 84.0 ± 8.9 mmHg. The mean of serum potassium, Scr, eGFR and UPCR were 4.17 mEq/L, 1.43 ± 0.55 mg/dL, 63.2 mL/min/1.73 m^2 and 1.88 ± 1.01, respectively (Table 1).

Aliskiren significantly showed the benefit in reducing UPCR at 2 and 24 weeks of the present study by 33 and 45 percent from baseline, respectively. Aliskiren were good to control blood pressure as shown in Fig. 1. The SBP were significantly decreased from 137.8 to 123.7 ($p = 0.01$) at 2 weeks, 137.8 to 126.26 ($p = 0.04$) at 4 weeks and 137.8 to 121.0 mmHg ($p = 0.002$) at 24 weeks of the present study, respectively. Similar to SBP, the DBP was significantly decreased from 84.08 to

Table 1. Baseline characteristics

Baseline Characteristics	Mean ± SD
Age (yr)	57.2 ± 11.0
Sex	
Male	11 (73.3%)
Female	4 (26.7%)
Height (cm)	166.8 ± 6.7
Weight (Kg)	76.3 ± 15.4
BMI (Kg/m^2)	27.2 ± 4.4
HbA1C (%)	7.95 ± 1.2
Smoking	0
Mean sitting BP (mmHg)	
Systolic	137.8 ± 17.6
Diastolic	84.0 ± 8.9
Urine protein-to-creatinine ratio	1.88 ± 1.01
Serum creatinine (mg/dl)	1.43 ± 0.55
Estimated glomerular filtration rate (ml/min)	63.2 ± 16.8
Serum potassium (mEq/l)	4.17 ± 0.53

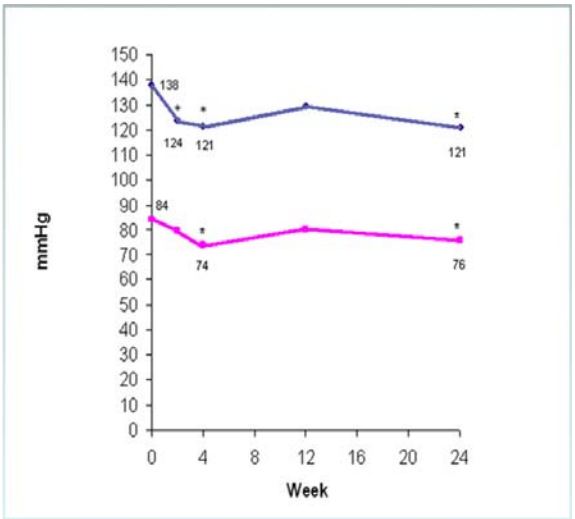

Fig. 1 Antihypertensive effect of aliskiren.
At second week after treatment, SBP decreased from 137.8 to 123.7 mmHg (p = 0.01) and DBP decreased from 84.06 to 79.33 mmHg (p = 0.24). At 4 week after treatment, SBP decreased from 137.8 to 121.26 mmHg (p = 0.04) and DBP decreased from 84.06 to 73.66 mmHg (p = 0.04) and at the end of study, SBP decreased from 137.8 to 121.0 mmHg (p = 0.002), DBP decreased from 84.06 to 75.85 mmHg (p = 0.002).
* Significant difference p ≤ 0.05 compared with the baseline

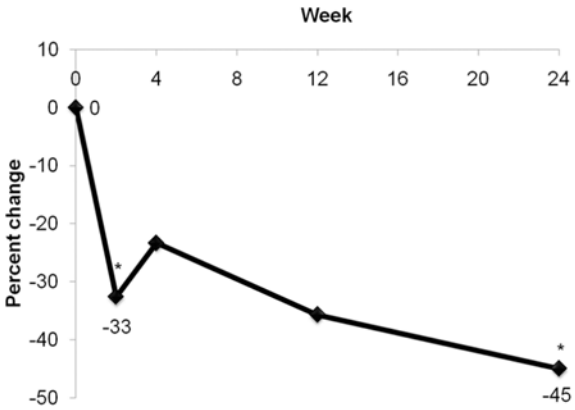

Fig. 2 Antiproteinuric effect of aliskiren.
UPCR after Aliskiren 150 mg administration for 2 weeks showed significantly decreased for 33% (p = 0.007). Following with Aliskiren 300 mg daily administration for another 22 weeks, UPCR declined for 45 % at the end of study (24 weeks) (p = 0.004).
* Significant difference p ≤ 0.05 compared with the baseline

79.33 (p = 0.24) at 2 weeks, 84.08 to 73.66 (p = 0.04) at 2 weeks and 84.08 to 75.85 mmHg (p = 0.002) at 24 weeks after the treatment. Reduction of UPCR showed significantly reduced for 32.65% (p = 0.007) and 45.0% (p = 0.004) from baseline at 2 weeks and 24 weeks after DRI treatment (Fig. 2). The mean serum creatinine was sligthly changed from 1.43 mg/dl to 1.56 mg/dl at 24 weeks (p = 0.22) (Fig. 3), the eGFR was dropped from 63.2 to 56.7 ml/min/1.73 m^2 (p = 0.13) (Fig. 4). Mean serum potassium was non significant rising from 4.17 to 4.31 mEq/ L (p = 0.34) (Fig. 5). Only 2 patients had adverse event, one patient developed hypotension and the other has gout attack during study.

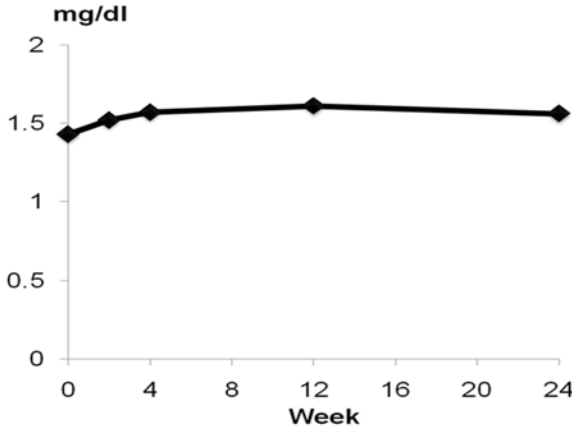

Fig. 3 Change from baseline in serum creatinine.
There was no significant change in mean serum creatinine at the end of study when compared with the baseline (p = 0.22)

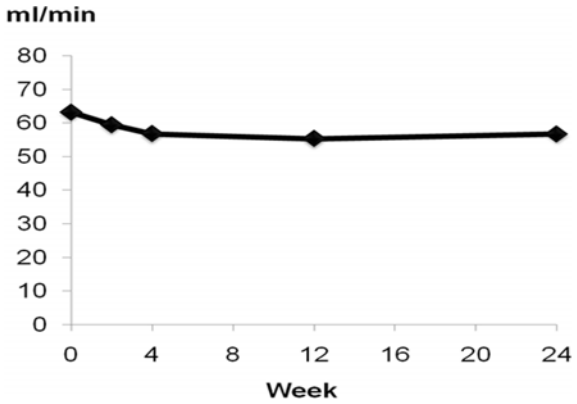

Fig. 4 Mean change in estimated glomerular filtration rate (eGFR).
There was no significant change in mean eGFR at the end of study when compared with the baseline (p = 0.13)

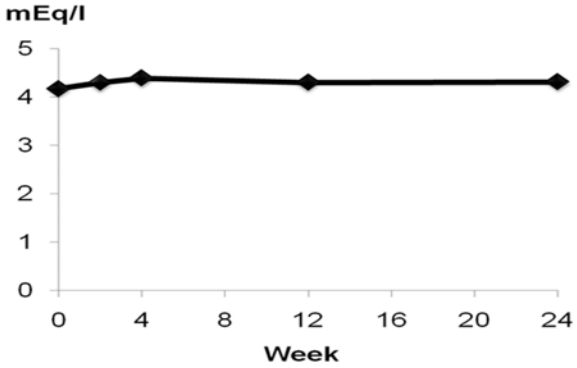

Fig. 5 Change from baseline in serum potassium.
The mean serum potassium showed no significant change at the end of study when compared with the baseline (p = 0.34)

Discussion

The growth rate of Type 2 DM is reaching epidemic proportions in many countries throughout the world. A number of different treatment modalities and medication have been evaluated to delay the progression of DN including ACEI, and ARB. Recently, aliskiren a direct renin inhibitor has also emerged as a potential therapeutic strategy to block the RAAS consequence lower blood pressure[9]. In present study, the authors demonstrated that treatment with aliskiren as monotherapy in overt DN showed strong efficacy on blood pressure control and proteinuria reduction.

Aliskiren monotherapy was proved to have benefit in blood pressure control in the present study. The blood pressure lowering effect of aliskiren was significantly existed since 2 week after treatment. The maximum efficacy in blood pressure lowering was presented at 4 week and continues to 24 week after treatment. Previous clinical trials compared the blood pressure lowering effects of aliskiren with ACEI. In hypertensive diabetic patients, aliskiren was equally effective in lowering mean DBP compared with ACEI[18]. A significantly greater reduction in SBP was seen in aliskiren treated patients. Similar results were obtained in long term comparison of aliskiren and ACEI in nondiabetic hypertensive patients also[17]. The similar result in blood pressure reduction was observed in aliskiren combination with ARB too[19]. All the previous clinical trials are concordance to effectiveness of aliskiren at 24 weeks of the present study to significantly reduced BP to target goals.

In the present study, aliskiren monotherapy significant showed its effectiveness in proteinuria reduction since 2 weeks after therapy. Moreover, aliskiren treatment has protein reduction by 45% at 24 week that similar to previous study[20,21]. In aliskiren compare with ACEI, sub-analysis in patients with proteinuria demonstrated that aliskiren based therapy significantly reduced UACR from baseline by 62% compare with 50% of ACEI[20]. Similar result in proteinuria reduction between aliskiren and ARB treatment was demonstrated from previous study[21]. Aliskiren monotherapy led to a significant reduction in albuminuria by 48% compared with placebo but not significantly different from ARB. Moreover combination therapies with DRI add on ARB showed mean UPCR ratio by 20% reduction by aliskiren monotherapy of 24 weeks. These data confirmed the benefit of DRI monotherapy to reduce proteinuria and achieved more benefit in combination treatment with ACEI or ARB.

No significantly changed in eGFR and SCr in our patients at the end of study compared with baseline. In clinical study of aliskiren compare with ARB and combination therapy in 26 DM type 2 patients, eGFR was significantly reduced 4.6 ml/min/1.73 m^2 by aliskiren, 8 ml/min/1.73 m^2 by ARB and 11.7 ml/min/1.73 m^2 by combination therapy[21]. eGFR changes seemed to be dependent on treatment and these reports showed DRI has less effect on hemodynamic than ARB. In fact, it has been shown that an early hemodynamic reduction in eGFR can translate into long-term renoprotection. Study in 599 DM type 2 patients treated with the combination of aliskiren and ARB for 6 months showed no significant change of eGFR[19]. According to previous clinical trails and our results, it could not clearly interpret the effect of aliskiren on eGFR. Therefore, long term studies and more number of patients must be conducted to elucidate the beneficial effect on the kidney on eGFR that is seen on short term period is sustained. There was no significant change in serum potassium elevation that proposes to be frequent adverse event. From the previous study aliskiren monotherapy or combination treatment showed slightly increase in serum potassium but no patients developed hyperkalemia[21].

In conclusion, aliskiren as monotherapy provide reduction in BP significantly in 2 weeks and maximum effect at 4 weeks. The protein reduction effect of aliskiren proved to be significant since first 2 weeks after treatment and maximum effect at 24 weeks. These results indicated that aliskiren monotherapy had effective BP lowering and great benefit in proteinuria reduction in diabetic nephropathy patients.

Potential conflicts of interest

None.

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ผลการรักษาด้วยยาเดี่ยว Direct Renin Inhibitor ต่อภาวะโปรตีนรั่วในปัสสาวะของผู้ป่วยโรคไตจากเบาหวาน

สมฤธัต ศิลารัตน์, แสงเดือน สำราญทรัพย์, สุดเขตต์ ด้วงชนะ, อดิศว์ ทัศณรงค์

ภูมิหลัง*: โรคไตจากเบาหวานเป็นสาเหตุสำคัญของการเกิดโรคไตเรื้อรัง และนำไปสู่ภาวะไตวายระยะสุดท้ายจากการศึกษาก่อนหน้านี้ พบว่าการยังยั้งระบบ RAAS โดยยากลุ่ม ACEI และ ARB สามารถลดโปรตีนในปัสสาวะ และชะลอการเสื่อมของไต ตามทฤษฎี DRI สามารถยังยั้งกระบวนการกระตุ้น RAAS ได้อย่างสมบูรณ์ โดยการลดระดับ PRA, Ang I, Ang II การศึกษานี้จึงมีจุดประสงค์เพื่อมุ่งมั่นค้นหาผลของการรักษาด้วยยาเดี่ยว Aliskiren ในการควบคุม ความดันโลหิต และลดปริมาณโปรตีนในปัสสาวะ*

วัสดุและวิธีการ*: ผู้ป่วยเบาหวานที่มีการทำงานของไตมากกว่า 30 มิลลิลิตรต่อนาทีต่อ 1.73 ตารางเมตร และปริมาณโปรตีนในปัสสาวะมากกว่า 300 มิลลิกรัมต่อวัน ที่สมัครใจเข้าร่วมการศึกษา ได้รับยา Aliskiren 150 มิลลิกรัมต่อวันใน 2 สัปดาห์แรกจากนั้นเพิ่มขนาดเป็น 300 มิลลิกรัมต่อวันจนครบ 24 สัปดาห์*

ผลการศึกษา*: ความดันโลหิต systolic ของผู้ป่วยลดลงจากเดิม 137.8 เป็น 123.7 มิลลิเมตรปรอท (p = 0.01) ที่ 2 สัปดาห์, 137.8 เป็น 126.26 มิลลิเมตรปรอท (p = 0.04) ที่ 4 สัปดาห์ และ 137.8 เป็น 121 มิลลิเมตรปรอท (p = 0.002) ที่ 24 สัปดาห์ เช่นเดียวกันความดันโลหิต diastolic ลดลงจากเดิม 84.08 เป็น 79.33 มิลลิเมตรปรอท (p = 0.24) ที่ 2 สัปดาห์, 84.08 เป็น 73.66 มิลลิเมตรปรอท (p = 0.04) ที่ 4 สัปดาห์ และ 84.08 เป็น 75.85 มิลลิเมตรปรอท (p = 0.002) ที่ 24 สัปดาห์ ส่วนปริมาณโปรตีนในปัสสาวะลดลงอย่างมีนัยสำคัญทางสถิติ ร้อยละ 32.65 (p = 0.007) และ ร้อยละ 45 (p = 0.004) ที่ 2 สัปดาห์ และ 24 สัปดาห์หลังการรักษาตามลำดับ ระดับซีรั่มครีเอตินีนหน้าที่ การทำงานของไต และซีรั่มโปแตสเซียม ไม่มีความแตกต่างจากระดับพื้นฐาน และไม่พบผลข้างเคียงของยาที่เป็นอันตรายต่อผู้ป่วยที่ได้รับยา aliskiren*

สรุป*: การรักษาด้วยยาเดี่ยว Aliskiren สามารถลดโปรตีนในปัสสาวะได้อย่างมีนัยสำคัญทางสถิติควบคุมความดันโลหิตได้ดีปราศจากผลข้างเคียงที่เป็นอันตราย ในผู้ป่วยโรคไตจากเบาหวานที่มีโปรตีนรั่วมากกว่า 300 มิลลิกรัมต่อวัน*