

Antiproteinuric Effect of Aliskiren versus Losartan in Primary Glomerulonephritis

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Abstract

Introduction: Treatment with renin-angiotensin-aldosterone-system (RAAS) blockers plays a major role in halting chronic kidney disease (CKD) progression. Aliskiren is the first orally available direct renin inhibitor (DRI). **Objective:** We studied the efficacy of aliskiren compared to losartan in patients with primary GN. **Design and Method:** This was a prospective open-label randomized control trial in patients with primary GN. Patients were randomized to receive either aliskiren or losartan to maximum tolerated doses for 24 weeks. Blood and urine investigations were measured at baseline and at 4-weekly intervals. Adverse effects were recorded. **Results:** 22 patients were recruited (aliskiren-11 and losartan-11). Their baseline characteristics were comparable with the exception of a higher proteinuria (uPCI) in the aliskiren arm. There were no significant differences in proteinuria, blood pressure and other renal parameters between both groups. At end-study, only patients in the aliskiren arm showed significant reductions in both the systolic blood pressure and in proteinuria. There were no changes in the other parameters of renal function over time and no adverse events occurred. **Conclusion:** Aliskiren appears to be as efficacious and tolerable as losartan both as an antihypertensive and antiproteinuric agent in this study.

Keywords

Primary Glomerulonephritis, Hypertension, Proteinuria, Aliskiren, Losartan

1. Introduction

Glomerulonephritis (GN) either primary or secondary is clinically manifested by proteinuria, hematuria, edema

with/without hypertension. The incidence of primary GN varies between 0.2/100,000/year and 2.5/100,000/year [1]. The commonest primary GN in Malaysia was minimal change disease (MCN, 33.4%), followed by focal segmental glomerulosclerosis (FSGS, 29.3%), Immunoglobulin A nephropathy (IgAN, 19.6%) and idiopathic membranous nephropathy (9.8%) [2]. Chronic GN is the third leading cause of end stage renal disease (ESRD) after diabetes mellitus and hypertension among Europeans [3], while in Malaysia it was reported that 30% of new ESRD to have underlying GN [4].

Proteinuria is an important predictor of outcome for ESRD in both diabetic nephropathy and primary GN [5]-[9]. The greater the proteinuria the faster the estimated glomerular filtration rate (eGFR) decline [10]. Treatment with renin-angiotensin-aldosterone-system (RAAS) blockers plays a major role in halting chronic kidney disease progression. They confer renoprotection by acting as both antihypertensive and antiproteinuric agents. It is well established that losartan has a significant antiproteinuric effect in diabetic nephropathy and this was also demonstrated in GN [11]-[15]. Notwithstanding this, a proportion of patients still progress to ESRD.

Aliskiren is the first orally available direct renin inhibitor (DRI) that acts at the initial activation step of the RAAS thereby reducing formation of angiotensin II by angiotensin converting enzymes (ACE) and ACE-independent pathways. Just like standard angiotensin-converting enzymes inhibitors (ACE-I) and angiotensin II receptor blockers (ARB), DRIs were shown to diminish renal vascular resistance and increase renal blood flow and would be expected to provide similar renoprotective benefits. The use of aliskiren as antiproteinuric agent in diabetic nephropathy as a single agent or add-on therapy to other RAAS blockers is controversial. There were limited data on antiproteinuric efficacy of aliskiren especially as single agent in patients with primary GN. Hence, the primary objective of this study was to evaluate the antiproteinuric effect of aliskiren compared to losartan in primary glomerulonephritis, the rationale for our study. Our secondary objective was to evaluate other parameters of renal function.

2. Methodology

2.1. Patients and Methods

This was a prospective open-label randomized control trial involving patients with primary GN on follow up at the Nephrology Unit, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The study approved by the University Ethics & Research Committee (FF-419-2011) and Malaysian National Medical Research Registry (11-778-10417).

Only patients with proteinuria of 0.3 g - 3.5 g/day and CKD stages 1 - 3 (eGFR > 30 ml/min/1.73 m²) with the diagnosis of primary GN were included in this study. Patients on stable maintenance immunosuppressive therapy were included without altering the immunosuppressive drug. All patients had blood pressure of ≤ 150/90 mmHg and serum potassium of < 5.5 mmol/L at recruitment. Patients with known renal artery stenosis or allergy to study drugs were excluded from this study. Pregnant or lactating patients and patients with childbearing potential without effective method of birth control were also excluded from this study.

2.2. Randomization

Patients who met the eligibility criteria were recruited. Prior to randomization patients who were on RAAS blockers underwent a 4-week washout period. Other antihypertensive medications were continued. The patients were reviewed 2-weekly during the washout period and target systolic blood pressure (SBP) ≤ 150 mmHg and diastolic blood pressure (DBP) ≤ 90 mmHg were maintained. Other antihypertensive medications were added and/or dose adjusted until target blood pressure was achieved. Randomization was done in blocks of four.

2.3. Study Protocol

At study entry, blood samples for renal, liver and lipid profiles were taken. Spot urine sample urine Protein Creatinine Index (uPCI) was also taken. The study duration was for 24 weeks. Patients were reviewed at Weeks 0 (baseline), 2 (V1), 4 (V2), 8 (V3), 12 (V4) and 24 (V5). At Weeks 4 (V2), 8 (V3), 12 (V4) and 24 (V5)-blood pressure, uPCI and blood investigations listed above were taken each visit except for the eGFR, and lipid parameters which were evaluated at the beginning (V0) and end of the study-Week 24 (V5).

Losartan and aliskiren doses were uptitrated to the maximum tolerated dose as judged by blood pressure. Losartan dosages ranged from 50 - 100 mg daily and those for aliskiren from 150 - 300 mg daily. Patients were

strongly advised to adhere to the study drugs given and to report any adverse reactions either by phone or during clinic visits. Patient compliance to study treatment was assessed by pill counts. Compliance was taken as adherence with medications $\geq 80\%$ of the time.

2.4. Statistical Analysis

All data were recorded and analyzed using the statistical package Statistical Package for the Social Sciences version 20 (IBM SPSS, Armonk, NY: IBM Corp). Results were expressed as median with interquartile range (IQR). The differences between two groups were analyzed using the Mann-Whitney-U test. Related data across time were analyzed using both the Wilcoxon Signed Rank test and the Friedman's test. Nominal and ordinal data were analyzed using Fisher's exact test. Nonparametric correlations were analyzed using Spearman's Rank Order Correlation. Binary logistic regression was used to analyze confounding variables. A p value of < 0.05 was considered significant.

3. Results

143 patients were screened and 60 patients were noted to be in complete remission with proteinuria < 0.3 g/day. Twenty three patients were excluded as they were not on stable immunosuppressive therapies, 17 patients had CKD above stage 3, five declined, four females had breast cancer, six females were pregnant, two patients were HepBsAg positive and another four were planning to get pregnant. Hence, only 22 patients were recruited with 11 randomized to receive aliskiren and 11 to losartan.

Baseline demographics and clinical characteristics were tabulated in **Table 1**. Baseline laboratory investigations were tabulated in **Table 2**. The median dose of aliskiren used was 300 (150 - 300) mg daily and losartan 100 (50 - 100) mg daily. Other concurrent medications were no difference in between both groups.

Table 1. Baseline demographics and clinical characteristics of the study groups.

Parameters	Aliskiren (n = 11)	Losartan (n = 11)	p value
Age (years)	41 (33 - 52)	44 (36 - 61)	0.224
Male	3 (13.6%)	8 (36.4%)	0.086
Female	8 (36.4%)	3 (13.6%)	
Weight (kg)	66.4 (61.0 - 76.0)	74.0 (56.0 - 83.0)	0.847
Height (cm)	164.0 (160.0 - 170.0)	170.0 (155.0 - 175.0)	0.973
Body mass index (kg/m ²)	22.24 (21.40 - 25.85)	25.43 (23.82 - 28.14)	0.203
Blood pressure in mmHg			
Systolic BP	133 (128 - 140)	140 (130 - 158)	0.356
Diastolic BP	80 (67 - 90)	80 (70 - 88)	0.716
Primary Glomerulonephritis			
Ig AN	9 (40.9%)	7 (31.8%)	1.0
FSGS	2 (9.1%)	3 (13.6%)	
Membranous	0 (0%)	1 (4.5%)	
Age at diagnosis (years)	32 (28 - 40)	38 (28 - 55)	0.189
Disease duration (years)	5 (2 - 7)	6 (3 - 9)	0.355
Baseline Co-Morbidities			
Hypertension	4 (40%)	7 (87.5%)	0.066
Dyslipidaemia	6 (60%)	5 (62.5%)	1.000
Smoking	1 (10%)	0 (0%)	1.000

Results in median (IQR), IQR: interquartile range; IgAN: IgA nephropathy; FSGS: Focal segmental glomerulosclerosis; p value < 0.05 is significant.

Table 2. Baseline laboratory parameters of the two study groups.

Parameters	Aliskiren (n = 11)	Losartan (n = 11)	p value
Haemoglobin (g/dl) (NR: 4.0 - 10.0)	13.3 (12.35 - 14.0)	13.25 (12.2 - 14.5)	0.742
Se urea (mmol/L) (NR: 2.5 - 6.4)	4.7 (3.9 - 5.7)	3.9 (3.3 - 5.5)	0.236
Se creatinine (umol/L) (NR: 62 - 106)	85 (72 - 108)	73 (66 - 112)	0.818
Se potassium (mmol/l) (NR: 3.5 - 5.0)	4.3 (4.0 - 4.5)	3.8 (3.8 - 4.0)	0.054
Se uric acid (umol/l) (NR: 149 - 450)	367 (306.5 - 401)	429 (292.7 - 507.7)	0.102
Se albumin (g/L) (NR: 35 - 50)	43 (40 - 45)	43 (41.7 - 44.5)	0.695
uPCI (g/mmol creat) (NR: <0.02)	0.10 (0.07 - 0.16)	0.05 (0.04 - 0.11)	0.043
CKD			
Stage 1	2 (9.1%)	4 (18.2%)	1.00
Stage 2	6 (27.3%)	5 (22.7%)	
Stage 3	3 (13.6%)	2 (9.1%)	
eGFR (ml/min/1.7m ²)	65 (57 - 73)	79 (56 - 105)	0.278

Results in median (IQR), IQR: interquartile range; uPCI: urine protein index; CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; p value < 0.05 is significant.

The changes in uPCI were tabulated in **Table 3**. There were no significant changes in serum creatinine, eGFR, serum potassium, uric acid levels and serum albumin in between both groups. The changes of blood pressure were tabulated in **Table 4**. Correlations between changes in uPCI and other variables such as blood pressure, serum creatinine, albumin and body mass index (BMI) were analyzed using Spearman's Rank Order Correlation. There was no significant correlation between uPCI with serum albumin, creatinine, BMI or DBP. There was significant correlation at week 12 between uPCI and SBP. However on further analysis with binary logistic regression, SBP was not a predictor for reduction in uPCI. There were no adverse effects seen during the 24 weeks study period. There was no hyperkalaemia or deterioration in renal function seen. All patients tolerated the drugs and were able to complete the 24 weeks study period.

4. Discussion

Many short term clinical studies in diabetic and non-diabetic chronic kidney disease (CKD) have shown that aliskiren as add-on therapy to standard a ACE-I and/or ARB reduced proteinuria by a further 20% - 70% [16]-[21]. Unfortunately the role of aliskiren in diabetic nephropathy was controversial following the results from ALTITUDE study that revealed adding Aliskiren to ACE-I or ARB caused higher adverse events which included non-fatal stroke, renal dysfunction and hyperkalaemia [22].

There were very few published studies on the antiproteinuric efficacy of aliskiren in patients with primary GN, hence the rationale for our study. In addition, ours was a head-to-head comparison of the antiproteinuric effect of aliskiren (DRI) to an ARB (losartan) in proteinuric primary GN patients.

The baseline laboratory parameters were comparable and statistically not significant with the exception of heavier proteinuria in the aliskiren arm. At the end of the study period of 24 weeks, the aliskiren group showed a significant 20% reduction of proteinuria compared to baseline. Of these, three out of the 11 patients achieved $\geq 50\%$ reduction of their baseline proteinuria. This result is comparable with other studies of similar duration such as AVOID (18%) in diabetic nephropathy [23], Tang *et al.* (22%) in IgA nephropathy [20] and Li *et al.* (26%) in non-diabetic CKD [19]. However these studies utilized aliskiren as add-on therapy to ARB and not as single agent as in our study.

A head-to-head comparison between aliskiren and perindopril (ACEI) by Lizakowski *et al.* was conducted in 14 patients with non-diabetic CKD [17]. After 12 weeks of either aliskiren or perindopril the patients were crossed over to the other arm for another 12 weeks of treatment after a 12-week washout period. The authors reported that treatment with aliskiren 300 mg/day reduced 24-h proteinuria by 36% compared to placebo. This

Table 3. Changes of uPCI with time for both study groups.

		Week 0	Week 4	Week 8	Week 12	Week 24	p value (intragp)
uPCI (g/mmol)	Aliskiren	0.10 (0.07 - 0.16)	0.065 (0.03 - 0.12)	0.07 (0.03 - 0.12)	0.07 (0.03 - 0.11)	0.08 (0.03 - 0.12)	0.033
	Losartan	0.05 (0.04 - 0.11)	0.05 (0.02 - 0.08)	0.05 (0.02 - 0.11)	0.04 (0.02 - 0.13)	0.03 (0.02 - 0.10)	0.736
p value (Intergp)		0.043	0.501	0.263	0.290	0.319	

Data expressed in median (IQR), IQR = interquartile range; $p < 0.05$ is significant. Intragroup: Using Friedman's two-way analysis; Intergroup: Using Mann-Whitney-U.

Table 4. Changes of blood pressure with time in both study groups.

BP		Week 0	Week 4	Week 8	Week 12	Week 24	p value (intra-gp)
Systolic BP	Aliskiren	133 (128 - 140)	129 (118 - 133)	124 (116 - 130)	121 (117 - 132)	123 (114 - 136)	0.013
	Losartan	140 (130 - 158)	128 (123 - 140)	130 (120 - 139)	130 (122 - 140)	130 (117 - 140)	0.432
	p value (inter-gp)	0.323	0.793	0.222	0.114	0.264	
Diastolic BP	Aliskiren	80 (67 - 90)	75 (66 - 86)	75 (65 - 80)	75 (66 - 81)	71 (62 - 83)	0.313
	Losartan	80 (70 - 88)	70 (68 - 86)	75 (70 - 88)	80 (70 - 90)	74 (70 - 80)	0.418
	p value (inter-gp)	0.716	0.817	0.428	0.197	0.448	

Data expressed in median (IQR), IQR = interquartile range; $p < 0.05$ is significant. Intragroup: Using Friedman's two-way analysis; Intergroup: Using Mann-Whitney-U.

was not different when compared with perindopril 10 mg/day which decreased proteinuria by 25%.

Persson *et al.* are the only other investigators who have conducted a head-to-head comparison between aliskiren monotherapy, irbesartan (ARB) monotherapy or combined aliskiren-irbesartan to placebo in Type 2 diabetic patients with nephropathy [16]. In this study aliskiren was as effective as irbesartan compared with placebo and reduced proteinuria by 48% and 58% respectively. The combination showed significant proteinuria reduction compared to either monotherapy as expected.

Thus, to our best knowledge, our study was the first head-to-head comparison of the antiproteinuric effect between a direct renin inhibitor and ARB in patients with primary GN.

A subanalysis of the study by Persson *et al.* reports that the optimal antiproteinuric dose for aliskiren is 300 mg daily with 48% reduction compared to placebo [24]. Studies by Parving *et al.* (AVOID) [23], Gupta *et al.* [25] and Lizakowski *et al.* [17] also titrated aliskiren dose to 300 mg daily. The median dose used for aliskiren in our study was 300 mg daily.

Multicentre trials have shown that the optimal antiproteinuric dose for losartan is 100 mg daily and that no additional benefit was seen beyond this dose [26]. However, other studies have also shown that losartan even at doses as low as 25 mg daily significantly reduces proteinuria as hypertension is not always present in cases of early non-diabetic CKD [12]. In our study, there was also "mild" proteinuria reduction in the losartan group at end study but this did not achieve significance [median 0.05 (0.04 - 0.11) g/mmol at baseline reducing to [0.03 (0.02 - 0.10) at end study; $p = 0.736$]. One reason for this is the small number of study patients. Another reason may be due to the even lower proteinuria in this group than that in the aliskiren group. Many studies have demonstrated that the degree of proteinuria reduction was proportional to baseline proteinuria—the higher the baseline proteinuria the greater the reduction [27]-[29]. Thus the negative finding in losartan group may be due to the small number of patients and low baseline proteinuria.

Although there were no differences in blood pressure between the two groups, aliskiren seems to be a more potent antihypertensive agent than losartan and the aliskiren group had a significantly lower systolic blood pressure. The efficacy of aliskiren as an antihypertensive has been reported in various clinical trials whether used as monotherapy or combination. Its antihypertensive effect has also been compared with various ARBs. These include valsartan, irbesartan and losartan. Aliskiren used in combination with valsartan provides significant additive and tolerable antihypertensive properties [30]. In another study, the antihypertensive efficacy of aliskiren 150 mg was found to be similar to irbesartan 150 mg daily [31]. Yet another study showed comparable antihypertensive effect between aliskiren 300 mg daily and losartan 100 mg daily [32].

In our study the antiproteinuric effect was independent of blood pressure control as patients' blood pressures were already near to target. Analysis using binary logistic regression showed that the reduction in proteinuria was independent of blood pressure or other variable. This is in agreement with that reported by many large studies where equivalent reductions in blood pressure could not account for the degree of proteinuria reduction or stability of renal function which led the authors to conclude that RAAS conferred renoprotection "beyond blood pressure reduction" [27] [33].

Aliskiren in a head-to-head comparison with losartan did not have any adverse effect on other renal function parameters. It was well tolerated and none of our patients developed any side effects. This concurs with previous studies that reported no adverse effects on renal function with aliskiren usage [17] [34].

5. Conclusion

Despite the small sample size, our study showed aliskiren to have comparable antiproteinuric and antihypertensive effects to ARB without any adverse effect on renal function which is well tolerated. Therefore it may be recommended that patients with primary GN who are intolerant to ACEIs or ARBs or have hypertension can be started on aliskiren. A large trial is indicated to confirm these preliminary findings.

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Conflict of Interest

None declared.

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