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RESEARCH ARTICLE

Aliskiren and Losartan Study in Non Diabetic CKD- A 3 Year follow up Study on Effects of Stopping Therapy

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ABSTRACT

Objective: The objective of this 6 year retrospective analysis of the therapeutic efficacy of Combined Aliskiren and Losartan is a follow up study to document the effects of stopping therapy after the initial 3 years of therapy.

Method: This is a 2nd Phase follow up study three years after the initial 1st Phase study. Patients in the 2nd Phase study were those who continued to have proteinuria and were treated with Losartan 100mg a day compared to those with no proteinuria on completion of the 1stPhase of the 6 year study. The 2ndPhase study seeks to document any untoward effects of cessation of therapy among the patients among these patients following their initial 1st Phase therapy for proteinuria.

Results: Among the 154 patients, 67/154 (44%) continued to have proteinuria, while 87/154 (56%) had no proteinuria (remission). Of these 87 patients, 43/154 (28%) had remission with no relapse for the 3 years and the other 44/154 (29%) had relapses. Withdrawal of therapy was associated with improvement in renal function and CKD staging.

Conclusion: A 3 year therapy appears to be a safe an adequate duration for ARB/Aliskeran therapy for proteinuria and though about a third (29%) may relapse, in the majority of cases, proteinuria was less than 0.5gm /day. There were no untoward effects of therapy withdrawal.

Introduction

In the treatment of Chronic Kidney Disease (CKD), many doctors do not discontinue their therapy with ARB, they would continue with the treatment because of concerns of rebound proteinuria or worsening of the renal function once they stop therapy. As an extension of our earlier study [1] of ARB and Aliskiren in non diabetic CKD, at end of 3 years, as continuation of the control study, those patients in remission with no more proteinuria stopped therapy and those who still had proteinuria were continued on losartan 100mg a day. All patients were continued on the trial for another 3 years to monitor effects of stopping therapy (2nd Phase Study). This study seeks to document the effects of stopping therapy for CKD patients after 3 years duration of treatment.

This study also documents the effects of stopping ARB/Aliskiren on eGFR, BP and CKD status. Some studies [2,3] have reported improvement in eGFR in those who stopped ARB as there is intraglomerular BP increase with withdrawal of ARB. The BP of the patients have also been reported to increase and these studies [2,3] reported an improvement of CKD staging as eGFR improves.

In our previous publication on the same topic we reported the effects on proteinuria when therapy was stopped [4] and when one should consider stopping therapy. Our present study reports on the other effects of stopping therapy apart from the effects on proteinuria and we hope that our experience may help to provide a guide as to when one should consider stopping therapy for patients with CKD rather than maintaining therapy indefinitely.

Subjects and Methods

In a database comprising 312 patients with Chronic Kidney Disease, 155 patients with CKD due to Chronic Glomerulonephritis and not due to diabetic nephropathy, hypertensive nephro sclerosis, lupus nephritis or Henoch Schonlein nephritis were recruited for the study. From 2007 to July 2012, data of these 312 patients were examined for the purpose of a retrospective study. Non biopsied CKD patients formed the bulk of our clinical practice and were more readily recruited. For purposes of standardization of the study, we decided to recruit only non biopsied patients into the study. In this new database for the purpose of this study, the database of 155 patients were selected, among which 51 patients were treated with combination therapy using an ARB (Losartan) and Aliskiren, 52 patients were treated with Aliskiren alone and the remaining 52 patients were treated with ARB (Losartan alone) as this was a retrospective study involving only patient medical records. Waiver of informed consent was obtained for all patients from the hospital's Institutional Review Board (IRB). Entry criteria included those patients who had been treated on the above drugs for at least 36 months within the 5 years period; other criteria included proteinuria of 1 gram or more and or Chronic Kidney Disease (CKD) Stage 3 at the start of the 36 months period. There were no significant differences in the various parameters between the 3 groups on entry into the study (Table 1). All selected patients had adequate control of BP control which was achieved with addition of atenolol, amlodipine or nifedipine.

For these 154 patients we had identified them for a 2nd Phase study with the intention of an additional 3 year follow up with regards to documenting when proteinuria returns in some (relapse) and in the others whether proteinuria disappeared completely (TUP $\leq$ 0.2 gm/day) for the next 3 years without any treatment (remission). For the other patients who continue to have proteinuria they were all treated with Losartan 100mg a day as a standard therapy and continued to be assessed every 6 months to completion of 3 years 2nd Phase follow up study (continuing proteinuria group). This practice follows the Department's guideline after the results of the ALTITUDE Trial [5-8] were released and HSA issued a note of caution to the use of combination therapy with Aliskiren and an ARB in view of the reported side effects and risk of hyperkalaemia. Following this, all patients in the Department ceased usage of Aliskiren and were prescribed Losartan as a substitute.

This is a 2nd Phase follow up study three years after the initial 1st Phase study [1]. Patients in the 2nd Phase study were those who continued to have proteinuria and were treated with Losartan 100mg a day compared to those with no proteinuria on completion of the 1st Phase of the 6 year study (remission). The 2nd Phase study seeks to document effects of stopping therapy among the patients who had achieved a remission of proteinuria following their initial 1st Phase study. One patient was lost to follow up leaving 154 patients for the 2nd Phase follow up study.

Study Design

All 155 patients on the database had the following investigations documented at six monthly intervals: serum creatinine, eGFR and Total Urinary Protein (TUP). Serum creatinine was quantitated with alkaline picrate and TUP

was quantitated by biuret agent. Glomerular Filtration Rate was estimated using the Cockcroft Gault formula for eGFR. Decrease in eGFR was expressed as ml of eGFR loss per year over the 6 year duration from time of entry to exit of the trial. Improvement in eGFR was taken as the positive difference between the entry eGFR and the exit eGFR over the study period. End stage renal failure was equated with decline of eGFR to CKD stage 5 with eGFR less than 15 ml/min/year. The primary end points were stage 5 CKD or end stage renal failure. The secondary end points were reduction of proteinuria by 50% and change in eGFR.

For the 1st Phase study, the 155 patients with CKD were on various combinations of Aliskiren with Losartan, Aliskiren alone or Losartan alone for a period of 3 years. In the 2nd Phase study, Losartan 100mg daily was the treatment for those patients who had persistent proteinuria following the end of the 1st Phase study.

The 2nd Phase follow up study was for three years after the initial 1st Phase study. Patients in the 2nd Phase study were those who continued to have proteinuria and were treated with Losartan 100mg a day compared to those with no proteinuria on completion of 1stPhase study.

At the end of 6 years from the beginning of the first control study at year 7, we have 3 groups of patients. Those in remission till end of 6 years (X, n= 43), those who were in remission at end of 3 years but had relapses during the subsequent 3 years (Year 4 to 7) referred to as the Relapsing Group (Y, n= 44) and the third group with continuing proteinuria (Z, n=67) who were on Losartan 100mg a day from end of year 3 (begin of year 4) till end of year 6 (beginning of year 7).

1. Sample size

Sample size calculation was based on the proportion of patients achieving 30% decrease in TUP with treatment of normal dose Aliskiren or normal dose Losartan. A second sample size calculation was done to compare the rate of 30% TUP decrease between a combination dose of ARB plus Aliskiren and Aliskiren alone. Assuming that the rate of TUP decrease to be 30% in the Normal dose ARB and Normal dose Aliskiren and 60% in the combination dose of ARB plus Aliskiren, the number of patients required in each group was 49 for a 2-sided test with alpha=0.05 and power of 80%. We expected the effects of combination dose of ARB plus Aliskiren to be about the same as that of High dose ARB. Sample size for 2ndPhase study is 154 patients as 1 patient was lost to follow up due to emigration.

2. Statistical methods

SPSS 10.1 for Windows was used for all analysis. Results were expressed as mean ± SD or median (range) or count (%). For univariate analysis, Pearson's chi-square test was used for comparing categorical data and ANOVA for comparing numeric data between the 3 treatment arms. ANOVA was followed by multiple comparison with Student-Newman-Keuls (SNK) range test whenever statistical significance was found between the 3 treatment arms as well as the three arms of patients with remission, relapse and continuing proteinuria.

Next, a doubly multivariate ANOVA (MANOVA) with repeated measures was used to test the effect of drug treatment on both eGFR and Total Urine Proteinuria (TUP). The dependent variables were eGFR and TUP measured at 7 time points, namely baseline and thereafter every year of the 6 years of the study. The between-subject factor was treatment group with 3 levels corresponding to Combination dose of ARB and Aliskiren, Aliskiren alone and ARB alone. This was repeated for the other 3 patient arms of remission, relapse and continuing proteinuria.Adjustment was made for the covariates of average systolic BP and average diastolic BP. Average blood pressures were calculated by taking the mean of all blood pressures while on medication (mean of blood pressures from year 1 to year 6). Within MANOVA, the effect of combination dose of Aliskiren and ARB on the outcomes of eGFR and TUP was compared with each of the other drug dosage groups by simple contrast comparison testing. Similarly, repeated contrast testing was done to obtain and compare the loss in eGFR in each year between the various drug groups. The same MANOVA was repeated for the three patient arms of remission, relapse and continuing proteinuria.

Plots of mean values of eGFR and TUP adjusted for covariates of systolic BP and diastolic BP were presented; so were the contrast estimates, their corresponding 95% confidence intervals and p-values for the comparison of eGFR and TUP between the levels of interest of the treatment group as well as the patients with remission, relapse and continuing proteinuria.

Results

Table 1 compares the demographic and clinical profile of patients treated with combined dose of Aliskiren and Losartan, Aliskiren alone and Losartan alone from year 1 to 6. The eGFR and TUP was significantly lower in all 3 arms before and after the trial and the decrease was not significantly different among the 3 arms for eGFR.

There were no patients with ESRF at the end of the study in all the 3 groups.

Figure 1 shows the distribution of Total Urinary Protein (TUP) over the years by treatment arm.TUP was lower at the end of the study in all 3 arms. The changes in TUP showed a reduction between the baseline and each year. At each time point except for baseline, TUP was lower for Combined Aliskiren and Losartan compared to Aliskiren alone ($p<0.05$).and by MANOVA the p value was <0.016. The TUP for Combined Aliskiren and Losartan compared to Losartan alone was not significantly different at each time point.

A Chi Square analysis of the 3 drug arms compared with the proportion (%) of patients in each of the groups, viz, remission, relapse and continuing proteinuria show that those patients treated with Combined Aliskiren and Losartan had more remissions (31%), most relapses (39%) and least number of patients with continuing proteinuria (30%) ($p<0.043$) as shown in Table 1.

Table 2 compares the demographic and clinical profile of patients with Remission (X), Relapse (Y) and Continuing Proteinuria (Z) from year 4 to year 7. The eGFR in all 3 groups continue to decline but there was no significant differencs between the 3 groups. There was a significant difference in the reduction of proteinuria in all 3 groups ($p<0.001$). At Year 7, the TUP was 0.1± 0.1 gm/day for those in remission (X), 0.4± 0.3 gm a day for those with relapses (Y) and 0.5± 0.5 gm a day for those with continuing proteinuria (Z) (p value < 0.001 by MANOVA).

The changes in Year 4 and 5 following withdrawal of therapy are shown in Table 3: For Group X (remission) as shown in Table 3, eGFR improved from 42±14 ml/min in year 4 to 43±14 ml/min in year 5, but this difference was not significant. For Group Y (relapse) eGFR improved from 42±13mls /min in year 4 to 43±13 ml/min in year 5 but this difference was also not significant.

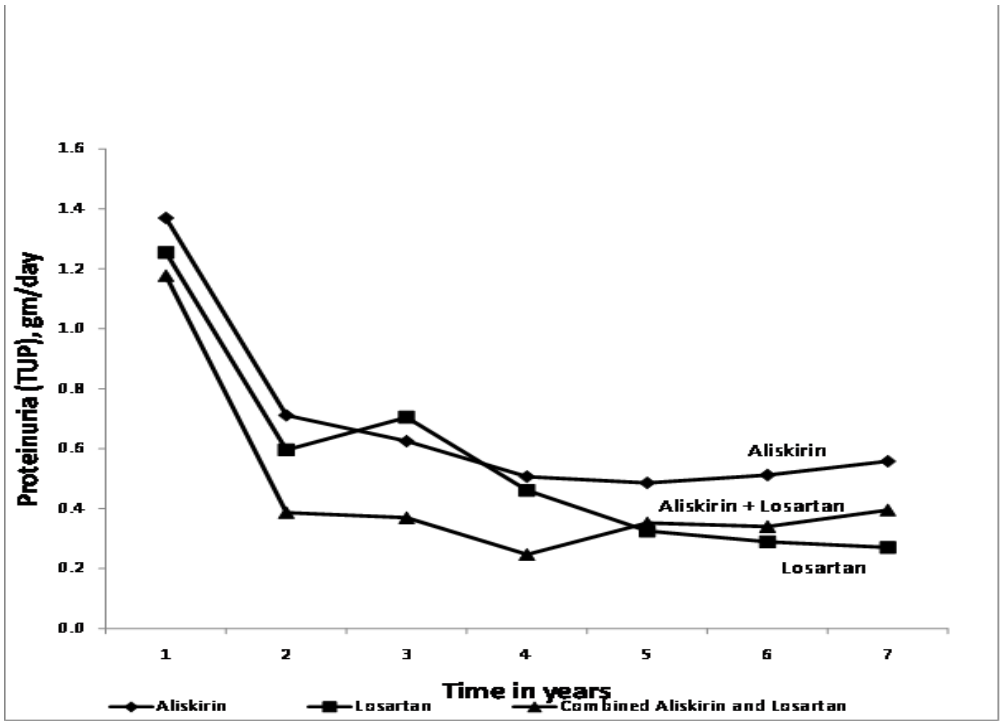

Figure 1: Shows the distribution of Total Urinary Protein (TUP) over the years by treatment arms.

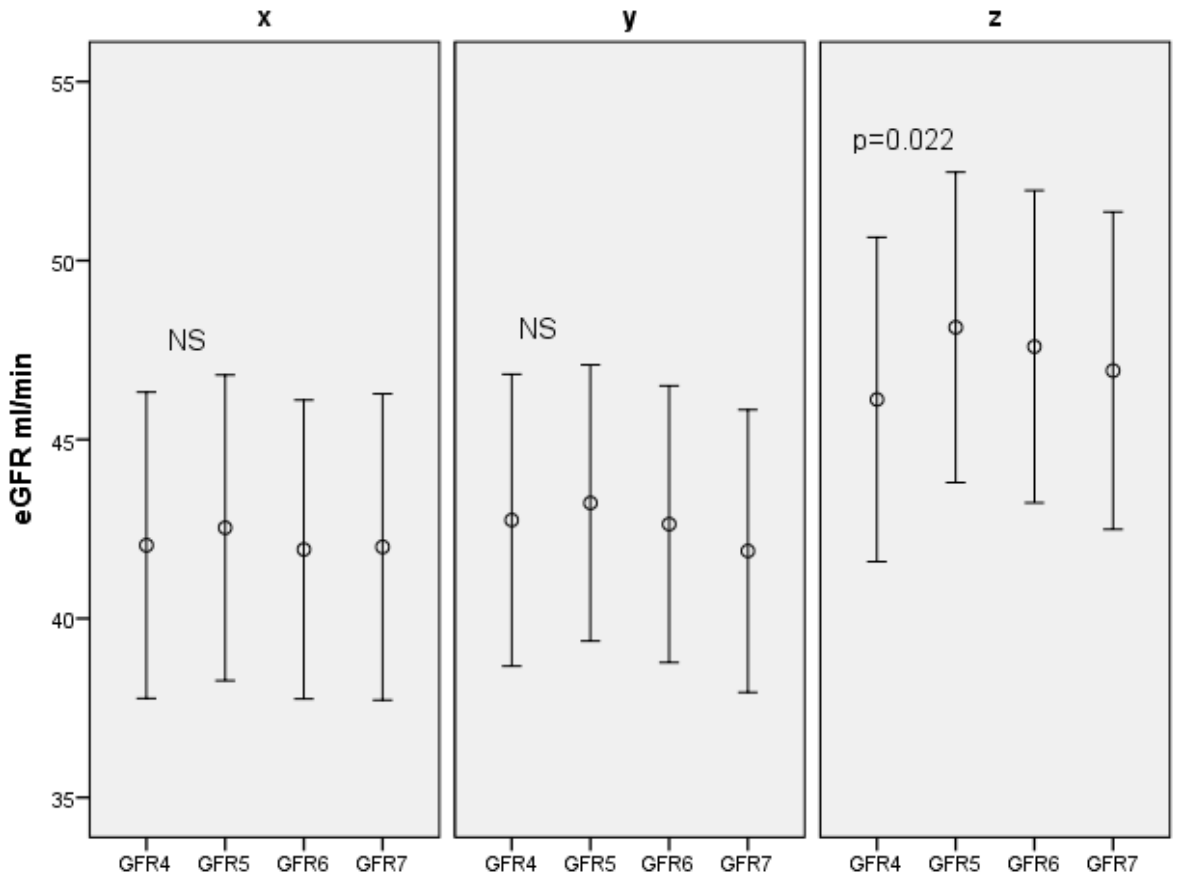

Figure 2: Shows the changes in eGFR from year 4 to year 7 for group X (Remission), Y (Relapse) and Z (Continuing Proteinuria).

In Group Z eGFR improved from 46±19 to 48±18 ($p<0.022$). This difference was significant. The changes in eGFR from year 4 to 7 are also shown in Figure 2.

As shown in Table 3, for Group X, Systolic BP increased from 133±13 to 136±12 ($p=0.026$) from year 4 to year 5. For Group Y Systolic BP increased from 130±10 to 132±12 ($p=0.449$). For Group Z Systolic BP increased from 130±11 to 132±10 ($p<0.049$).

For Group X, Diastolic BP decreased from 85±7 to 84±7 ($p=0.105$). For Group Y, Diastolic BP decreased from 85±6 to 83±7 ($p=0.123$). For Group Z Diastolic BP remained at 83±7 to 84±7 ($p=0.97$). The changes in diastolic BP were not significant.

For Group X, CKD statusimproved from 3.14±0.60 to 3.00±0.535 ($p=0.083$) from year 4 to year 5, but this difference was not significant. For Group Y, CKD status improved from 3.41±0.542 to 3.09±0.362 ($p<0.001$). For Group Z, CKD status improved from 3.01±0.6 to 2.91±0.6 ($p<0.034$).

Discussion

Whenever patients stop their ARB intake, their eGFR will improve as the intraglomerular BP increases because the efferent glomerular arteriolar vasoconstriction due to ARB is restored so the single nephron eGFR is increased again as in glomerular hyperfiltration and the overall eGFR increases or "improves" [2].

Table 1 - Comparing demographic and clinical profile of patients treated with Combined dose Aliskerin and ARB, Aliskerin alone and ARB alone (Year 1 to 6).

	Aliskerin n = 52	ARB n = 51	Combined Aliskiren and ARB n = 51	*p value
Sex (F: M) count (%)	36: 16 69% : 31%	30 : 21 59% : 41%	32 : 19 63% : 37%	0.540
Age at Diagnosis (Years)	52 ± 11	54 ± 12	52 ± 9	0.348
Duration of Trial (Months)	37 ±2	38± 2	37±3	0.677
Comorbidities, count (%)				
Hypertension	20 (39%)	29 (57%)	23 (45%)	0.166
Hypercholesterolaemia	22 (42%)	34 (67%)	25 (49%)	0.038
IHD	6 (12%)	7 (14%)	10 (20%)	0.495
EGFR (ml/min)				
Year 0	47± 13	49± 14	48± 12	0.769
Year 6	41 ± 14 (p<0.001)	46 ± 18 (p=0.001)	45 ± 15 (p=0.012)	0.189
Urinary Protein (gm/day)				
Year 0	1.4± 0.7	1.3± 0.6	1.2± 0.7	0.316
Year 6	0.6± 0.6 (p<0.001)	0.3± 0.3 (p<0.001)	0.4± 0.4 (p<0.001)	0.016
Blood Pressure (mmHg)				
Systolic, Year 0	138± 10	133± 14	134± 11	0.071
Systolic, Year 6	129 ± 9 (p<0.001)	130 ± 9 (p=0.253)	130± 10 (p<0.086)	0.758
Diastolic, Year 0	86 ± 7	85±8	86±7	0.676
Diastolic, Year 6	82 ± 5 (p<0.001)	82 ± 5 (p=0.044)	80±6 (p<0.001)	0.304
Improvement in eGFR	15 (29%)	15 (29%)	17 (33%)	0.866
Response:				
Remission"x"	15 (29%) 15 (29%)	12 (23%)	16 (31%)	0.043
Relapse "y"	22 (42%)	9 (18%) 30 (59%)	20 (39%)	
Continuing Proteinuria "z"			15 (30%)	

Continuous data are presented as mean ± SD and categorical data as count (%).

In our study, there is an increase or improvement of the eGFR in both the group with remission (X) and the group with Relapse (Y) though not statistically significant. However for the group with continuing proteinuria (Z), even though one would not expect an improvement in the eGFR since the patients are still on ARB Losartan, the eGFR improved significantly, to our surprise when we expected no change in eGFR.

The increase in Systolic BP in groups X and Y and Z was also consistent with that of other reports [2,3] since the effect of ARB is also to lower BP. In all 3 groups, the diastolic BP decreased but this was not statistically significant.

All three groups had improvement in CKD status which was consistent with the increase in eGFR. This improvement was significant in group Y and Z but not in X, the group with remission.

The question that remains is why the group with continuing proteinuria still on treatment with Losartan had significant improvement in eGFR at Year 5 of therapy. The answer to this can be found in our previous study on the effects of high dose Losartan therapy in IgA nephritis where we showed that patients with proteinuria with IgA nephritis after being treated with high dose

Table 2 - Comparing demographic and clinical profile of patients with Remission, Relapse and Continuing Proteinuria (Year 4 to 7).

	Remission (x) n = 43	Relapse (y) n = 44	Continuing Proteinuria (z) n = 67	*p value
Sex (F: M) count (%)	25: 18 58% : 42%	27 : 17 61% : 39%	46 : 21 69% : 31%	0.499
Age at biopsy (Years)	57 ± 10	53 ± 11	49 ± 10	0.003
Total Duration of Follow-up (Months)	74 ± 3	74 ± 2	73 ± 2	0.013
Hypertension (Yes : No)	16 (37%)	21 (48%)	35 (52%)	0.301
EGFR (ml/min)				
Year 4	42±14	42± 13	46± 19	
Year 5	43± 14	43± 13	48± 18	
Year 6	42± 14	43± 13	48± 18	
Year 7	42 ± 14	42 ± 13	47 ± 18	0.144
	(p=0.911)	(p=0.341)	(p=0.179)	
Urinary Protein (gm/day)				
Year 4	0.1± 0.04	0.2± 0.1	0.8± 0.5	
Year 5	0.1± 0.1	0.4± 0.2	0.5± 0.4	
Year 6	0.1± 0.1	0.4± 0.3	0.5± 0.5	
Year 7	0.1± 0.1	0.4± 0.3	0.5 ± 0.5	< 0.001
	(p<0.001)	(p<0.001)	(p<0.001)	
Blood Pressure (mmHg)				
Systolic, Year 4	133± 13	130± 10	130± 11	
Systolic, Year 5	136± 12	132± 12	132± 10	
Systolic, Year 6	132± 10	129± 9	129± 9	
Systolic, Year 7	131 ± 10	129 ± 8	130 ± 9	0.170
	(p=0.335)	(p=0.620)	(p=0.852)	
Diastolic, Year 4	85± 7	85± 6	83± 7	
Diastolic, Year 5	84± 7	83± 7	84± 7	
Diastolic, Year 6	82± 6	82± 7	82± 6	
Diastolic, Year 7	81 ± 6	81 ± 6	82 ± 5	0.730
	(p=0.001)	(p=0.004)	(p=0.399)	
Distribution of CKD at year 6				0.128
CKD 1	0 (0.0%)	0 (0.0%)	1 (1.5%)	
CKD 2	4 (9.3%	1 (2.3%)	13 (19.4%)	
CKD 3	30 (69.8%)	35 (79.5%)	44 (65.7%)	
CKD 4	9 (20.9%)	8 (18.2%)	9 (13.4%)	
Distribution of CKD at year 7				0.202
CKD 1	0 (0.0%)	0 (0.0%)	1 (1.5%)	
CKD 2	6 (14.0%)	4 (9.1%)	17 (25.4%)	
CKD 3	31 (72.1%)	29 (65.9%)	39 (58.2%)	
CKD 4	6 (14.0%)	11 (25.0%)	10(14.9%)	
Improvement in eGFR Yr 4 to Yr 5	22 (51.2%)	17 (38.6%)	33 (49.3%)	0.434
Improvement in eGFR Yr 5 to 6	20 (46.5%)	21(47.7%)	29 (43.3%)	0.238
Improvement in eGFR Yr 6 to 7	23 (53.5%)	18 (40.9%)	35 (52.2%)	0.412
Improvement in eGFR Yr 4 to 7	18 (41.9%)	20 (45.5%)	30 (44.8%)	0.936
Arm previously allocated to:				
Aliskiren alone	15 (35%)	15 (34%)	22 (33%)	0.043
Losartan alone	12 (28%)	9 (21%)	30 (45%)	
Combined Aliskiren and Losartan	16 (37%)	20 (45%)	15 (22%)	

Continuous data are presented as mean ± SD and categorical data as count (%). * p-value are from chi-square test for categorical data andrepeated measures ANOVA test for continuous data compared between the 3 groups over whole duration of years 4 to 7.

Losartan for 5 years were found to have an improvement in their eGFR [9]. Other workers [10-12] using Telmisartan, Valsartan and Irbesartan have also reported improvement in eGFR with high dose ARB therapy after treatment for about 5 years, similar to what we reported with High dose Losartan in IgA nephritis [8]. However in our study [9] we also showed that the feature of gain in eGFR also occurred inpatients on normal dose ARB losartan (100mg a day) and normal dose ACEI enalapril (20mg a day) but in both instances the gain in eGFR was significantly less than in the high dose losartan group. In the present study it is interesting that after year 5 going to Year 6 and 7, the gain in GFR in Group Z was not sustained and the eGFR in year 7 was less than in Year 6. Ahmed et al. [2] have also reported that the gain in eGFR in their patients was sustained for only 2 years, similar to our present study.

Why does Group Z with continuing proteinuria have improvement in eGFR while still on Losartan 100mg a day, though this is a short term improvement which was not sustained. This was contributed by dual therapy as well as the continuing normal dose of Losartan 100mg which was not present in groups X and Y, the two groups which had stopped therapy by end of year 3. The continuing dose of losartan plus previous high dose in some of those in Group Z contributed to the increase in eGFR which was not sustained as the effects wore off. This temporary increase in eGFR was not sustained with the discontinuation of high dose ARB present in 22% of these patients.

Our data also demonstrated that eGFR can improve in the presence of continuing proteinuria (Group Z), but the proteinuria was less than 1 gm a day in the majority of patients in this group, mean 0.8 gm/day at year 4 and 0.5 gm day at year 7 ($p<0.001$). TUP was <0.2 gm a day in Group X and Y at year 4.

Recovery or regression of glomerulosclerosis has been reported by Fogo et al [13]. In the early 1990s, Marinides [14] had reported reversal of proteinuria and glomerulosclerosis by combining a low protein diet with an ACE inhibitor in the puromycin aminoglycoside rat model. Adamazak [15] documented reversal of glomerulosclerosis after high dose enalapril treatment in subtotally nephrectomized rats. In another study, Ma [16] employing ACEI and or ARB in rats with subtotal nephrectomy showed decrease of glomerulosclerosis. Treatment was initiated 8 weeks after inducing renal injury. Four weeks later, sclerotic lesions were shown to decrease on autopsy.

We would suggest that stopping ARB therapy after 3 years is acceptable. One can stop ARB after 3 years once proteinuria has remitted. The question is, when patient relapses at what level of proteinuria should we restart ARB? We would perhaps recommend restarting ARB therapy when there is a relapse of proteinuria > 1 gram a day.

Is improvement in proteinuria always correlated with improvement in renal function? Many workers have found this to be so [17,18]. However this may not always be the case as shown in our previous study with ARB therapy [19], as well as our present study. In group Z, despite proteinuria the patient's hadmore increase in eGFR compared to X (remission group) and Y (relapse group). Our data would suggest that for those patients where there is no more proteinuria or where proteinuria is less than 0.5 gm a day, after a course of ARB therapy for about 3 years, one could stop ARB therapy.

Recently, Ahmed et al [2] examined the impact of stopping ACEI/ARB in patients with CKD 4-5 among their patients attending a low clearance clinic. In their report of 56 patients, mean age 73.3 years, referred for anticipation of renal replacement therapy, their ACEI/ARB was stopped. The eGFR of these patients increased from 16.38 ml/min to 26.6 ml/min after 12 months of stopping ACEI/ARB. A total of 61.5% of these patients had increase in eGFR by more than 25% 12 months after stopping therapy. This persisted in most patients for up to 24 months. Twenty five % of patients changed their CKD status from CKD 5 to 4 and 19% from CKD 4 to 3. The whole observation group was divided into 3 subsets, Group 1 where eGFR increased by 25%, Group 2 where eGFR deteriorated by 25% and group 3 where there was no significant change. Systolic BP increased from 134 to 139 mmHg and diastolic BP increased from 69 to 72 mmHg. There was no significant change in proteinuria.

Table 3. Comparing demographic and clinical profile of patients with Remission, Relapse and Continuing Proteinuria (Year 4 and 5)

	Remission (x) n = 43	Relapse (y) n = 44	Continuing Proteinuria (z) n = 67	*p value
Sex (F: M) count (%)	25: 18 58% : 42%	27 : 17 61% : 39%	46 : 21 69% : 31%	0.499
Age at biopsy (Years)	57 ± 10	53 ± 11	49 ± 10	0.003
Total Duration of Follow-up (Months)	74 ± 3	74 ± 2	73 ± 2	0.013
Hypertension (Yes : No)	16 (37%)	21 (48%)	35 (52%)	0.301
EGFR (ml/min)				
Year 4	42± 14	42 ± 13	46± 19	0.397
Year 5	43± 14 (p=0.56)	43± 13 (p=0.781)	48± 18 (p=0.022)	0.435
Urinary Protein (gm/day)				
Year 4	0.1± 0.04	0.2± 0.1	0.8± 0.5	<0.001
Year 5	0.1± 0.1 (p<0.001)	0.4± 0.2 (p<0.001)	0.5± 0.4 (p<0.001)	
Blood Pressure (mmHg)				
Systolic, Year 4	133± 13	130± 10	130± 11	0.270
Systolic, Year 5	136± 12 (p=0.026)	132± 12 (p=0.449)	132± 10 (p=0.049)	
Diastolic, Year 4	85± 7	85± 6	83± 7	0.444
Diastolic, Year 5	84± 7 (p=0.105)	83± 7 (p=0.123)	84± 7 (p=0.97)	
Distribution of CKD at Yr 4				
CKD 1	0 (0%)	0 (0%)	1 (1.5%)	0.082
CKD 2	5 (11.6%)	1 (2.3%)	11 (16.4%)	
CKD 3	27 (62.8%)	24 (54.5%)	41 (61.2%)	
CKD 4	11 (25.6%)	19 (43.2%)	14 (20.9%)	
Distribution of CKD at year 5				
CKD 1	0 (0.0%)	0 (0.0%)	1 (1.5%)	0.110
CKD 2	6 (14.0%)	1 (2.3%)	14 (20.9%)	
CKD 3	31(72.1%)	38 (86.4%)	42 (62.7%)	
CKD 4	6 (14.0%)	5 (11.4%)	10 (14.9%)	
Comparing CKD Yr 4 and 5				
Mean CKD Yr 4	3.14	3.41	3.01	0.02
Mean CKD Yr 5	3.00 (0.083)	3.09 (0.001)	2.91 (0.034)	
Improvement in eGFR Yr 4 to 5				
Yes	23	35	35	0.022
Stable	4	5	7	
No	16	4	25	
Arm previously allocated to:				
Aliskiren alone	15 (35%)	15 (34%)	22 (33%)	0.043
Losartan alone	12 (28%)	9 (21%)	30 (45%)	
Combined Aliskiren and Losartan	16 (37%)	20 (45%)	15 (22%)	

Continuous data are presented as mean ± SD and categorical data as count (%). * p-value are from chi-square test for categorical data andrepeated measures ANOVA test for continuous data compared between the 3 groups over whole duration of years 4 and 5.

There are some reservations that stopping ACEI/ARB may hasten decline of renal function but here the observation is the reverse. For most patients, initial therapy will decrease eGFR during the first 6 weeks but after this, the eGFR may increase and in the long term those on ACEI/ARB will have lesser degree of eGFR loss compared to those not on therapies. But if ACEI/ARB therapy is stopped, eGFR will improve as the decrease in intraglomerular BP due to ACEI/ARB is lifted off and there is therefore overall renal function improvement.

Conclusion

Our present study suggests that a 3 year therapy appears to be an adequate duration for therapy for proteinuria and though about one third of patients (29%) may relapse, in the majority of cases, proteinuria was less than 0.5gm a day in these patients. Our study suggests that patients in remission should consider stopping ARB therapy as present data have shown that this is safe and there are no untoward effects. There is therefore no necessity for maintenance of therapy indefinitely in the many cases where there is no significant proteinuria beyond 3 years.

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