Case Series

ATRA Therapy Restores Normal Renal Function and Renal Reserve and Prevents Renal Failure

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Abstract

This article presents clinical data which suggest that the current dosage of losartan 50 to 100 mg/day may not be the optimum in many cases, especially if used as monotherapy in the treatment of proteinuria and we may have to increase to 200 mg/day. However, about 30% of patients cannot take angiotensin-converting enzyme inhibitor (ACEI) because of the side effect of cough. To potentiate the anti-proteinuric effect of losartan, especially for patients who do not adhere to a low salt diet, a 12.5-mg dose of hydro-chlorothiazide may further decrease proteinuria. The main message of this article is that we would have to, in many instances, increase the dose of losartan to a minimum of 100 mg/day or 100 mg twice a day for some patients for optimal therapy. The second message is to monitor the creatinine clearance test (CCT) and to start therapy when CCT is reduced and not wait for serum creatinine to rise to abnormal levels (renal impairment) before starting therapy. The first group involves half a dozen patients with hypertension but no proteinuria. Therapy with losartan is shown to improve the renal function. This data suggest that losartan, apart from its use in reduction of proteinuria, can be used in patients with mild renal impairment without proteinuria to reverse the mild renal impairment and preserve renal function. The second group deals with 3 patients with low creatinine clearance. After a follow-up period of an average of 3 years, they all developed renal impairment. In another 6 patients, the data suggest that we should perhaps treat patients with low CCT as soon as possible and with dose ranging from 100 to 200 mg/day if necessary, to derive maximum beneficial effect. The third group highlights 5 patients with high CCT due to glomerular hyperfiltration. With time, the high CCT decreases and renal impairment sets in. The data suggest that patients with high CCT should be treated early to prevent renal impairment. The fourth group illustrates 6 patients where their proteinuria was markedly reduced with the increase of losartan from 100 mg/day to 200 mg/day, suggesting that losartan 200 mg/day is probably the optimum dose. In conclusion, apart from its traditional usage in reduction of proteinuria to retard progression to renal failure, the data suggest that losartan is also indicated in patients with renal impairment in the absence of proteinuria; patients with low CCT, patients with high CCT and patients who do not respond to a dosage of 100 mg/day should have the dosage increased to 100 mg twice daily to increase efficacy of losartan. It is hoped that with these new and earlier indications as well as increased dosage of losartan starting with 100 mg, whenever possible, and increasing to 200 mg/day, if there is no response, we can prevent more patients from developing renal failure. Based on these observations, further randomised controlled trials should be designed to address these issues.

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Key words: Angiotensin receptor antagonist, Creatinine clearance, Hyperfiltration, Kidney failure, Renal reserve

Introduction

In a previous study,[1] we reported that patients who had decreased proteinuria also had improvement in renal function. Three out of the 8 patients who had renal impairment prior to angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ATRA) therapy regained normal renal function after therapy with ACEI/ATRA, while the remaining 5 had improvement of renal impairment. However, there were 2 patients who had no decrease in proteinuria and still experienced reversal of their mild renal impairment (level of proteinuria remained the same after therapy with ACEI/ATRA).

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In this article, we present 4 hypotheses in relation to therapy with losartan, an ATRA which we elucidated as a therapeutic agent for various aspects of renal preventive therapy.

The first hypothesis is that losartan therapy can reverse mild renal failure irrespective of the effects of losartan as an anti-proteinuric or anti-hypertensive drug, i.e., even in patients with no proteinuria, the renal failure can be reversed.

The second hypothesis is that since losartan therapy can reverse renal failure, traditionally interpreted as reversing abnormally raised serum creatinine to normal levels, losartan should also be able to improve low creatinine clearance in patients even before the serum creatinine level becomes abnormal, i.e., losartan therapy should be able to improve and restore renal reserve.

The third hypothesis is that in glomerular hyperfiltration, elevated creatinine clearance levels may precede proteinuria and losartan therapy can restore high creatinine clearance to normal values even in the absence of proteinuria.

The fourth hypothesis is that contrary to popular practice, 100 mg daily dosage of losartan is not the maximum dose and that a dose beyond 100 mg/day up to 200 mg/day may confer better therapeutic response and renal protection.

Patients and Methods

Patients were pre-selected to fulfil certain criteria such as those with controlled essential hypertension, diabetic nephropathy, glomerulonephritis (GN) with renal impairment alone, in the absence of proteinuria, or those with low creatinine clearance or high creatinine clearance alone, without proteinuria.

Exclusion criteria included all patients with uncontrolled hypertension or those on ACEIs. There was no randomisation involved as patients have to be selected to fulfil certain inclusion criteria and recruited into 1 of the 4 groups. There were control groups in the first 2 groups, but in the last 2 groups the patients served as their own control group as their results were compared with those before the change in therapy. Altogether, 32 patients were recruited; 12 in the first group, 9 in the second, 5 in the third and 6 in the fourth study.

Results were expressed as mean ± SD and a two-tailed paired *t*-test was used to compare differences in the means in the same patients before and at the end of the study.

I. Patients with Essential Hypertension with Renal Impairment

Based on our earlier observations[1] of a previous control trial of patients with IgANx, we have decided to do a prospective study. We compare the renoprotective effect of ATRA (losartan) in a group of patients with essential hypertension and mild renal impairment (hypertensive nephrosclerosis) in the absence of significant proteinuria with a group of patients with essential hypertension and renal impairment but with proteinuria >1.5 g/day. Both groups of patients had their blood pressure (BP) controlled with hypotensive agents (beta blockers or calcium channel blockers) at the time of entry into the study. None of the patients in both groups were prescribed ACEI but were given losartan 50 mg/day, increasing to 100 mg/day at 6 monthly intervals if there was no decrease in proteinuria or improvement in renal function in those with proteinuria. In patients with essential hypertension with no proteinuria, losartan was increased from 50 mg/day to 100 mg/day if there was no improvement in renal function.

Table 1 shows the profile and results of ATRA therapy in the group of 6 patients with hypertensive nephrosclerosis but with no significant proteinuria. All 6 patients had significant improvement in renal function, with 4 of them reverting to normal renal function. The paired *t*-test for this group of patients was significant ($t = 3.04$, $P < 0.03$).

It is noted that even though patient 4 did not have hypertension nor proteinuria, the uninephrectomy he underwent could induce some form of hyperfiltration injury giving rise to nephrosclerosis with renal impairment. There was no doubt that improvement in his renal function was due to losartan, as stopping the medication caused the serum creatinine to become abnormal and reinstitution of losartan at a smaller dose of 25 mg/day reversed the mild renal failure.

Table 2 shows the profile of 6 patients with hypertensive nephrosclerosis with proteinuria >1.5 g/day. Although only 1 of the 6 patients had improvement in renal function, 5 had improvement in proteinuria. The paired *t*-test for the serum creatinine before and after treatment ($t = -1.6$, $P = 0.10$) was not significantly worse even though 5 out of 6 patients had slight worsening of the renal function.

II. The Problem of Low Creatinine Clearance

As nephrologists, we often focus on serum creatinine and proteinuria in the follow-up of our patients. Some of us do not order the creatinine clearance test (CCT) and even if we do, we choose to ignore low creatinine clearances attributing it to incomplete collection of urine.

However, if a patient repeatedly have low creatinine clearances, even though the serum creatinine values may be normal, it is a matter of time before the serum creatinine values become abnormal. Table 3 shows low creatinine clearances in 3 patients where the serial serum creatinine eventually became abnormal. They were treated for proteinuria with losartan in doses of 50 mg/day. Despite this, the patients still developed renal impairment. However, their diabetes mellitus and hypertension were well controlled.

Table 1. Hypertension With No Proteinuria

No	Sex/Age (y)	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	M/67	EssHPT wHN	36	20	140/80	140/80
2	M/74	EssHPT wHN	30	22	130/80	140/75
3	M/62	EssHPT wHN	42	16	120/80	130/80
4	M/81	CaKidney/HF	36	-	120/80	120/80
5	F/68	EssHPT wHN	30	14	120/80	130/70
6	M/83	EssHPT	20	23	140/70	145/80
N			6	5	6/6	6/6
Mean			32	19	128/78	134/78
±SD			8	4	10/4	9/4
Paired *t*						-2.9/0.3
P						0.03/ns

No.	SCr1	SCr2	CCT1	CCT2	TUP1	TUP2	Treatment (mg)
1	168	155	33	34	0.2	0.17	Am5, At50, L50
2	177	139	30	36	0.1	0.1	At50, L50
3	150	128	46	83	0.17	0.2	Am5, L100
4	178	141	24	30	0.15	0.1	Am5, L50
5	166	137	33	37	0.1	0.1	L25
6	262	175	18	22	0.3	0.2	L100
N	6	6	6	6	6	6	
Mean	184	148	31	35	0.18	0.15	
±SD	40	15	10	9	0.08	0.05	
Paired *t*		3.04		-5.6		1.6	
P		0.03		0.003		ns	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

Table 2. Hypertension With Total Urinary Protein >1.5 g

No	Sex/Age (y)	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	M/74	EssHPT wHN	36	21	140/80	130/80
2	M/64	EssHPT wHN	42	15	150/90	140/90
3	M/70	EssHPT wHN	36	12	130/70	130/80
4	M/72	EssHPT wHN	30	18	120/70	130/80
5	F/61	EssHPT wHN	36	12	140/80	130/80
6	M/55	EssHPT wHN	42	13	140/90	150/80
N			6	6	6/6	6/6
Mean			37	15	137/80	135/82
±SD			5	4	10/9	8/4
Paired *t*						-0.5/0.4
P						ns/ns

No.	SCr1	SCr2	CCT1	CCT2	TUP1	TUP2	Treatment (mg)
1	147	173	40	33	2.3	0.91	Am5, L50
2	208	259	30	22	2.1	1.7	At100, Am10, L100
3	128	285	37	16	1.9	1.2	At50, L50
4	144	162	36	32	2.3	2.6	At50, L50
5	186	211	23	21	2.1	0.8	Am10, L100
6	182	155	40	43	1.7	0.4	Am10, A100
N	6	6	6	6	6	6	
Mean	166	208	34	28	2.1	1.3	
±SD	31	54	7	10	0.2	0.8	
Paired *t*		-1.6		1.96		2.9	
P		ns		ns		0.03	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

These 3 patients were compared with another 6 patients (Table 4) where losartan was given in a dose of 100 mg/day for low creatinine clearance to determine if there was a difference in response with regards to low creatinine clearance.

All 3 patients in Table 3 with low creatinine clearance eventually developed renal failure with increased serum creatinine after an average of 3 years despite therapy with losartan 50 mg/day. In contrast, in the group of 6 patients in Table 4 given losartan 100 mg/day, all 6 patients had improvement in creatinine clearance. This difference was significant (pair $t = -3.3$ $P < 0.02$).

III. The Problem of High Creatinine Clearance

High creatinine clearance with or without proteinuria in a patient with kidney disease with previously normal creatinine clearance signifies glomerular hyperfiltration. This is related to angiotensin II induced vasoconstriction which occurs in the course of progression of the renal disease. Five patients (Table 5) with high creatinine clearance due to glomerular hyperfiltration were treated with losartan 100 mg/day to reduce the high creatinine clearance. All 5 patients had increased creatinine clearance (>150 mL/min) over a period of 12 to 18 months before starting losartan therapy. These 5 patients therefore served as their own controls.

At the end of the treatment period all 5 patients had their high creatinine clearance reduced to normal levels. This difference was significant (paired $t = 4.3$, $P < 0.013$).

IV. The Maximum Dose of Losartan to Reduce Proteinuria

The recommended maximum dose for losartan is 100 mg/day. Table 6 shows the profile of 6 patients who were treated with losartan 100 mg/day for proteinuria for a period of 1 to 3 years with no decrease in proteinuria. When proteinuria eventually worsened despite therapy with losartan 100 mg/day, the dose was increased to 200 mg/day. These 6 patients therefore served as their own control group.

All 6 patients responded with a dramatic decrease in proteinuria (paired $t = -3.1$, $P < 0.026$).

Patient 1 had IgA nephritis and for 3 years had been treated with losartan 100 mg/day, but his proteinuria was always above 2 g/day. He could not tolerate ACEI because of cough. Losartan was increased to 200 mg/day and the proteinuria progressively decreased to 0.06 g/day.

Patient 2 also had IgA nephritis with nephrotic range proteinuria which did not respond to prednisolone and neoral cyclosporine A. He could not tolerate ACEI. Despite losartan 100 mg/day, the proteinuria was always above 3 g/day. When losartan was increased to 200 mg/day, proteinuria progressively decreased from 5.4 to 1.4 g per day.

Patient 3 had diabetic nephropathy and hypertension. Her proteinuria was around 2 g/day when she was prescribed losartan 100 mg/day. When it rose to 4.9 g a day, losartan was increased to 200 mg/day. Proteinuria progressively decreased to 0.32 g. She had low creatinine clearance with progressive renal impairment which was reversed. One could argue here that it was the progressive glomerulosclerosis due to progressive renal failure which caused the decrease in proteinuria and not the ATRA therapy. It was probably a combination of both but by July 2004, the renal failure did improve (serum creatinine 142 from 186 micro m/L).

Patient 4 had diabetic nephropathy and hypertension. He could not tolerate enalapril. His proteinuria was 6.83 g with decreased creatinine clearance, 56 mL/min. Since his BP was also high, he was prescribed losartan 200 mg/day. The proteinuria reduced to 0.06 g with creatinine clearance increasing to 82 mL/min.

Patients 5 and 6 were on losartan 100 mg/day for 3 years and 27 months, respectively, and proteinuria decreased significantly only when losartan was increased to 200 mg/day.

Discussion

I. Essential Hypertension (HPT) with Renal Impairment

In the 6 patients mentioned in Table 1, going by traditional practice and evidence based medicine, they had no significant levels of proteinuria or uncontrolled hypertension which would warrant the use of losartan, an ATRA. However, based on the results of our earlier clinical trial,[1] where we demonstrated that treatment with losartan could reverse mild renal impairment without influencing proteinuria, we instituted therapy with losartan in doses varying from 50 to 100 mg/day and all patients had significant improvement of renal function with 4 of them (66%) normalising the renal function.

In contrast, in the 6 patients with essential hypertension with proteinuria exceeding 1.5 g/day, therapy with losartan in daily doses of 50 mg to 100 mg did not improve renal impairment except in 1 patient. Five out of these 6 patients had improvement in proteinuria (paired $t = 2.9$, $P = 0.03$).

Our data showed that ATRA can independently improve renal function in the absence of proteinuria, suggesting that aside from improvement in renal function through decrease of proteinuria, other beneficial effects through other mechanisms are possible with the use of ATRA. These mechanisms could include preservation or improvement of the glomerular architecture[2,3] through remodelling of the

Table 3. Low Creatinine Clearance on Losartan 50 mg

No	Sex/Age	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	M/56	Diabetic nephropathy	57	27	160/80	130/80
2	F/52	Diabetic nephropathy	34	3	150/70	135/80
3	M/65	Diabetic nephropathy	58	5	140/80	140/80
N	3		3	3	3/3	3/3
Mean	57.7		49.7	11.63	150/76.7	135/80.0
±SD	6.7		13.6	13.3	10/5.8	5/0
Paired *t*	-		-	-		1.7/-1.0
P	-		-	-		115/115

No	SCr1	SCr2	CCT 1	CCT 2	TUP 1	TUP 2	Treatment (mg)
1	137	176	50	37	1.73	2.3	Am5, L50
2	128	158	47	33	3.6	4.9	Am5, L50
3	113	154	59	52	1.7	0.3	At50, L50
N	3						
Mean	126.0	162.7	52.0	40.7	2.3	2.5	
±SD	12.1	11.7	6.2	10.0	1.1	2.3	
Paired *t*		-10.8		5.2		-0.2	
P		0.008		0.035		ns	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

Table 4. Low Creatinine Clearance on Losartan 100 mg

No	Sex/Age (y)	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	F/61	Diabetic nephropathy	48	Nil	120/80	120/80
2	F/45	IgA nephritis	36	Nil	120/70	110/70
3	F/73	Diabetic nephropathy	38	Nil	144/80	135/75
4	F/52	Diabetic nephropathy	7	12	145/80	145/80
5	F/67	Diabetic nephropathy	6	20	130/80	130/80
6	M/46	Diabetic nephropathy	6	11	145/80	140/80
N	6		6			
Mean	57		24	7	133/78	130/78
±SD	12		19	8	12/4	13/4
Paired t	-		-	-		2.0/1.0
P	-		-	-		0.1/ns

No	SCr1	SCr2	CCT 1	CCT 2	TUP 1	TUP 2	Treatment (mg)
1	66	69	55	72	0.06	0.06	L100
2	105	104	65	75	0.64	0.06	L100
3	75	68	68	128	0.1	0.06	L100
4	82	74	67	86	1.14	0.06	Am5, L100
5	105	90	60	78	0.48	0.06	At50, L100
6	138	11	52	75	0.06	0.06	At50, L100
N	6	6	6	6	6	6	
Mean	95	86	61	86	0.41	0.06	
±SD	26	19	7	21	0.43	0	
Paired *t*		2.1		-3.3		2.0	
P		0.09		0.02		0.1	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

Table 5. Effects of Losartan on High Creatinine Clearance

No	Sex/Age (y)	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	M/50	IgA nephritis	53	5	150/80	140/80
2	M/49	Chronic glomerulonephritis	46	8	140/75	130/70
3	M/67	Diabetic nephropathy	49	Nil	145/80	140/80
4	M/41	Diabetic nephropathy	7	5	140/80	145/85
5	M/50	Chronic glomerulonephritis	24	7	140/90	130/80
N	5		5	5	5	5
Mean	51		36	5.0	143/81	137/79
±SD	10		20	3.1	4/5	7/5
Paired *t*	-		-	-		2.1/0.8
P	-		-	-		ns/ns

No	SCr1	SCr2	CCT 1	CCT 2	TUP 1	TUP 2	Treatment (mg)
1	93	89	217	178	0.56	0.27	Am5, L100
2	70	77	186	151	1.02	0.25	At50, L100
3	100	103	178	105	0.71	0.58	L100
4	75	78	220	204	1.18	1.15	Am10, L100
5	82	88	196	161	1.79	0.78	Am5, L100
N	5	5	5	5	5	5	
Mean	84	87	199	160	1.05	0.61	
±SD	12	11	19	37	0.48	0.38	
Paired *t*		-1.6		4.3		2.35	
P		ns		0.013		0.079	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

Table 6. Response of Proteinuria to Losartan 200 mg/day

No	Sex/Age (y)	Diagnosis	FU (mo)	HPT (y)	BP1	BP2
1	M/29	IgA nephritis	23	Nil	130/80	120/80
2	F/59	IgA nephritis	28	Nil	140/80	130/80
3	F/61	Diabetic nephropathy	49	8	140/70	140/70
4	M/59	Diabetic nephropathy	12	9	130/80	125/80
5	M/75	Diabetic nephropathy	37	Nil	140/80	135/80
6	F/50	IgA nephritis	27	Nil	110/70	120/70
N	6		6	6	6	6
Mean	56		29	2.8	132/77	128/77
±SD	15		13	4.4	12/5	8/5
Paired *t*			-	-		1.1
P			-	-		*ns*

No	SCr1	SCr2	CCT 1	CCT 2	TUP 1	TUP 2	Treatment (mg)
1	108	129	116	123	2.1	0.06	L200
2	122	128	65	74	5.4	1.4	L200
3	186	142	39	65	2.1	0.36	Am5, L200
4	114	113	56	82	6.83	0.06	At50, L200
5	148	150	58	59	3.94	1.76	L200
6	66	65	90	107	1.12	0.72	L200
N	6	6	6	6	6	6	
Mean	123	121	71	85	3.6	0.7	
±SD	40	30	28	25	2.2	0.7	
Paired *t*		0.3		-3.3		3.1	
P		ns		0.020		0.026	

Am: amlodipine; At: atenolol; BP: blood pressure; CCT: creatinine clearance test; FU: follow-up; HPT: hypertension; L: losartan; mo: months; ns: not significant; SCr: serum creatinine; SD: standard deviation; TUP: total urinary protein; y: years

GBM (improvement in pore selectivity being one of them),[3,4] reducing transforming growth factor-β (TGF-β) and thereby reducing or reversing glomerular sclerosis[4] or other mechanisms which remodel the glomerulus and restore function.[4-6]

II. The Problem of Low Creatinine Clearance

Low creatinine clearance is often ignored in the follow-up of renal patients. The low values are often dismissed as due to incomplete collection of urine by the patients. To address this, the Cockroft-Gault formula[7] has been used to calculate the creatinine clearance without the need of a 24-hour urine collection which could be tedious for the patient and fraught with inaccuracy of improper urine collection.

Clinicians therefore prefer to focus on serum creatinine and total urinary proteinuria as more reliable markers for monitoring the progress of patients. But from our data, we have shown that low creatinine clearance with normal serum creatinine do end up with the patient manifesting abnormal serum creatinine after an average of about 3 years of follow-up in the 3 cases illustrated (Table 3). In these 3 patients, though they were treated with losartan 50 mg/day there was no improvement in renal function, perhaps because they were treated late and the dose of losartan was only 50 mg/day.

In Table 4, in the 6 cases where the only abnormality was low creatinine clearance in the presence of normal serum creatinine and no significant proteinuria, all 6 were treated early with losartan 100 mg/day and all had improved creatinine clearance (paired t = -3.3, P <0.02). There is suggestion from this data that patients with low creatinine clearance with normal serum creatinine and no proteinuria should be treated with losartan 100 mg as starting dose.

III. The Problem of High Creatinine Clearance

High creatinine clearance levels in the presence of significant proteinuria, with or without abnormal serum creatinine levels, are attributed to glomerular hyperfiltration.[8,9] There is suggestion from those data that patients with high creatinine clearance due to glomerular hyperfiltration could benefit from losartan therapy to induce normal creatinine clearance.

IV. The Maximum Dose of Losartan

The recommended therapeutic dose of losartan is 100 mg/day.[10] Even in large multicentre trials[10,11] and our earlier trial,[1] the maximum dose of losartan prescribed was 100 mg/day as the thinking then was that there was no additional beneficial effect from losartan beyond a dose of 100 mg/day.

However, as demonstrated in the 6 patients (3 with IgA nephritis and 3 with diabetic nephropathy) mentioned in Table 6, all had a dramatic reduction of proteinuria when a daily dose of 200 mg of losartan was prescribed. It is interesting to note here that in the case of patient 3, she had diabetic nephropathy with established renal failure and with losartan 200 mg/day, the renal failure could be reversed over a period of 4 years.

The present data suggest that we should not be using an ATRA only to reduce proteinuria or retard progression to renal failure. In this study, there appears to be evidence that ATRA therapy can normalise not only raised serum creatinine but also normalise low or high creatinine clearance, i.e. ATRA therapy can restore not only normal renal function (serum creatinine) but also restore loss of renal reserve (creatinine clearance).

In a recent publication,[1] we have also demonstrated that ACEI/ATRA used in patients with IgA nephritis (IgANx) decreases proteinuria and those patients who respond with decrease in proteinuria also had the proteinuria converted from non-selective to selective proteinuria. This improvement in protein selectivity is related to the ability of these agents to reduce the radii of the larger shunt pathway on the glomerular basement membrane (GBM). These larger shunt pathways are those which allow the passage of larger molecular weight (MW) protein (non-selective proteinuria) compared to those with smaller shunt with correspondingly smaller radii that only allow the passage of smaller MW protein like albumin (selective proteinuria).[3]

The ability of ATRA to reduce the larger shunt pathways to the smaller shunt pathways (conversion of non-selective to selective proteinuria) suggests that some form of remodelling is occurring within the glomerulus as a result of the ATRA therapy.

Recent studies have also demonstrated that ACEI, apart from remodelling the GBM (the improvement in pore selectivity being one of the end results), may also have beneficial effects on the mesangial cells by decreasing TGF-β production, thereby decreasing mesangial matrix production, hence ameliorating the disease process in IgAN and in diabetic nephropathy where there is mesangial cell proliferation.[12] In addition, ATRA has been shown to exert an antiproliferative effect on mesangial proliferative glomerulonephritis.[13] This could help to explain further the improvement in renal function in patients with IgAN on ACEI/ATRA therapy. In order for this to occur, the injury must be still at the stage in which it is possible for amelioration of the renal lesions and possibly remodelling of the renal architecture. Patients with more advanced renal disease with glomerulosclerosis and thickening of the GBM are less likely to respond to therapy with improvement in selectivity index and serum creatinine. In this respect, we

found that patients with serum creatinine exceeding 300 micro m/L are less likely to recover renal function, though therapy with ATRA may retard their long-term progression to end-stage renal failure.

In terms of restoring normal renal function, we should think in terms of not only normalising raised serum creatinine levels but also normalising creatinine clearance levels (in those cases where it is low or high as in patients with decreased renal reserve or those with hyperfiltration). With regard to the treatment of proteinuria, it is not enough to reduce proteinuria to <1 g/day or even <0.5 g/day, we should target for the disappearance of proteinuria i.e. to 0.15 or 0.06 g/day when the patient is considered to have no proteinuria at all. In this respect, this concept is akin to bringing a patient's BP to normal levels and normal may be lower than 120/80.

If one were to accept the above concepts, it would mean embracing the principles of the 4 hypotheses mentioned in the introduction with regards to ATRA therapy, viz, the first hypothesis referring to normalising raised serum creatinine levels and hence reversing renal failure, the second and third to normalise low and high creatinine clearance levels in reference to decreased renal reserve and glomerular hyperperfusion and the fourth to reduce proteinuria using a maximum dose of 200 mg/day of losartan targetting at the disappearance of proteinuria. In this respect, it is worthwhile to report that of the 6 patients given a dose of losartan 200 mg/day, 2 of them eventually had disappearance of proteinuria to levels <0.06 g/day.

Conclusion

In conclusion, our data based on the above studies suggest that it may be useful to offer ATRA therapy to the following groups of patients with:

1. Renal impairment (except for those with renal artery stenosis) alone or in the presence of proteinuria.
2. Low creatinine clearance, alone or in the presence of proteinuria.
3. High creatinine clearance, alone or in the presence of proteinuria.
4. For patients who have not achieved the desired therapeutic response with respect to improvement of mild renal impairment, decrease in proteinuria, improvement in low creatinine clearance or desired decrease in high creatinine clearance the maximum dose of losartan could be increased to 200 mg/day.

Based on these observations, further randomised controlled trials should be designed to address these issues.

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