World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers © All Rights Reserved
Available online at: http://www.wjpsonline.org/
Review Article

Renoprotection with antihypertensive effect by inhibition of rennin - angiotensin system

Mohd Urooj[1], Monika Tandon[2] and Sunil S. Iyer[3]

[1]Regional Research Institute of Unani Medicine MOH Aligarh India
[2]Department of Clinical Pharmacology Unit, Ranbaxy Laboratories Ltd, India
[3]Department of Clinical Pharmacology & Pharmacokinetic Unit Ranbaxy Laboratories Ltd, India

Received: 02-07-2014 / Revised: 14-07-2014 / Accepted: 26-07-2014

ABSTRACT

Hypertension is a common cause of chronic kidney disease (CKD) and even more common sequelae of CKD. It is essential to preserve renal function while controlling blood pressure. There is growing evidence that reduction and normalization of proteinuria is a key treatment goal for renal protection. Several clinical studies, mainly but not exclusively in diabetic patients were reviewed, subsequently suggested that anti-hypertensive agents inhibiting the renin– angiotensin system (RAS), such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), achieved better renoprotection than other anti-hypertensive drugs. Inhibition of the renin-angiotensin system (RAS), either by ACE inhibitors or angiotensin-Receptors blocker (ARB) slows the progression of CKD by reducing the level of proteinuria in the diabetic and non-diabetic CKD resulting in less renal structural damage.

Keywords: Chronic kidney disease, Renin angiotensin system, Angiotensin receptors blocker. Angiotensin-converting enzyme inhibitor,

INTRODUCTION

In pioneering studies, Mogensen [1] and Parving et al. [2] have demonstrated that anti-hypertensive treatment slowed the decline of renal function in hypertensive patients with diabetic nephropathy. Several clinical studies, mainly but not exclusively in diabetic patients, have subsequently suggested that anti-hypertensive agents inhibiting the renin–angiotensin system (RAS), such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), achieved better renoprotection than other anti-hypertensive drugs [3,4].

A genetic predisposition to hypertension increases the risk to develop CKD. Parents of type 1 diabetic patients had higher BP values than parents of patients without diabetic nephropathy [5]. Higher BP values were found in parents of type 1 diabetic patients with as compared to parents of patients without diabetic nephropathy [6]. Ambulatory BP measurement revealed higher BP values in offspring of type 2 diabetic patients with as compared to offspring of type 2 diabetic parents without diabetic nephropathy [7].

Thus, the treatment of hypertension has become an important component in the treatment of most CKD patients not only to prevent cardiovascular complications but also to protect the kidney [8, 9]. Meta-regression analyses have indicated that BP reduction accounts for 50% of the variance in glomerular filtration rate (GFR) decline and that each 10- mmHg reduction in mean arterial pressure (down to 92 mmHg) confers a benefit in GFR preservation of 3.7-5.0 ml/min per year [10-13].

Renin-Angiotensin System Inhibition

ACE inhibitors prevent the formation of angiotensin II by blocking the activity of angiotensin converting enzyme in RAS pathway. Similarly angiotensin II receptor antagonists inhibit the RAS at the level of the angiotensin II type 1 receptor, thereby providing effective antihypertensive effect [14]. Among a variety of anti-hypertensive, numerous randomized,

***Corresponding Author Address:** Mr. Mohd. Urooj Regional Research Institute of Unani Medicine MOH Aligarh India; qaziurooj@gmail.com*

controlled clinical trials have demonstrated that inhibitors of the RAS, i.e. angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) ameliorate the progression of CKD [15,16]. Although some studies utilizing BP radiotelemetry showed renoprotection by ACEi or ARB was completely BP dependent in animal models, these observations do not exclude a role for the RAS blockade-mediated, BP independent mechanisms. There is ample evidence both in primary renal disease and in nephropathy of type 1 and type 2 diabetes that pharmacological blockade of the RAS by ACEi or ARB has BP-independent renoprotective effects [17, 18].

RAS Inhibition in Diabetic Nephropathy

Diabetes-related nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of ESRD (End Stage Renel Disease) [19]. Persistent microalbuminuria has been shown to be a marker for the development of nephropathy in patients with type 2 disease. Additionally, microalbuminuria is well established as a marker for CVD risk. It is clear that inhibition of the renin-angiotensin system (RAS) is useful in slowing down the progression of nephropathy in patients with demonstrable microalbuminuria. Infact, the American Diabetes Association (ADA) is clear in recommending the use of RAS inhibition (with converting enzyme inhibitors or ARBs) in non-pregnant type 2 diabetic patients with microalbuminuria [19].

Remuzzi G [20] et.al conducted a study (BENEDICT study) reported that the use of the ACE inhibitor trandolapril in hypertensive, nor-moalbuminuric patients with type 2 diabetes was associated with a reduction in the development of diabetic nephropathy. Similarly Lewis EJ [21] et.al and Parving HH [2] et.al conducted a randomized clinical trial which shows that ARBs can reduce the rate of progression from microalbuminuria to macroalbuminuria and to ESRD in patients with type 2 diabetes.

Two high-quality, randomized studies compared reduction of ESRD in type 2 diabetic patients treated with ARB vs placebo. Brenner [22] and colleagues performed double blind randomized controlled studies enrolling 1513 type 2 diabetic patients with nephropathy in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. The primary end point was the composite of the double of serum creatinine, ESRD, and death. Losartan showed a 16% reduction in the composite primary end point (*95% CI, 2 to 28*). While 25.5% of the placebo group reached a primary end point of ESRD, only 19.6% of the patients treated with losartan developed ESRD (relative risk reduction, 28% (*95% CI, 11 to 42*). These effects were independent of BP, which was similar in the two groups throughout the study.

There are several randomized controlled clinical studies (list shown in Table 1) which clearly demonstrates that inhibition of RAS either by ACEi or ARB is a key treatment goal for renal protection beyond B.P reduction.

KIDNEY PROTECTION BY INHIBITION OF RAS

All these experimental and clinical studies show BP independent renoprotective effects of ACEi and ARB. Recent researches have focused on mechanisms of protection of the kidney by inhibition of RAS. ACEi and ARB have each been shown to reduce glomerular capillary pressure and ameliorate glomerular hyperfiltration effectively [14]. Pharmaceutical reagents that block RAS reduce oxidative stress in the kidney. Inhibition of RAS has direct immunomodulatory effects [23-25]. Potential mechanisms of renoprotective effects of ACEi and ARB are listed below.

Renoprotective Mechanisms of ACEi and ARB

- Decrease of systemic BP
- Amelioration of glomerular hypertension and hyperfiltration
- Reduction of oxidative stress
- Direct immunomodulatory effects
- Reduction of proteinuria
- Improvement of oxygenation of the tubulointerstitium

CLINICAL IMPLICATION

Hypertension is a common coexisting condition among patients with CKD as either the primary etiology or as a secondary event. Epidemiological data have convincingly shown that blood pressure (BP) is linked to CKD [26, 27] and kidney disease-related mortality. Results of large-scale, randomized studies (shown above) support that Inhibition of the renin-angiotensin system (RAS), either by ACE inhibitors or angiotensin-Receptors blocker (ARB) slows the progression of CKD by reducing the level of proteinuria in the diabetic and non-diabetic CKD resulting in less renal structural damage.

Acknowledgement: I express my gratitude to supervisors for their excellent and valuable assistance during review process.

Table 1: Clinical Trial/Study showing Renoprotective effect of ARB and ACEi

Trial/Study	Design	Subjects	No.	Drug	Dose	Primary End Point	Result
RENAAL	multicenter double-blind randomized placebo controlled	Type 2 diabetic patients with nephropathy	1,513	Losartan	50–100 mg	Doubling of serum creatinine level, ESRD, or death	ARB superior to placebo
ORIENT	multicenter double-blind randomized placebo controlled	Type 2 diabetic patients	577	olmesartan	10–40 mg	Doubling of serum creatinine level, ESRD, or death	ARB superior to placebo
MARVAL	multicenter double-blind randomized Active controlled	Type 2 diabetes and microalbuminuria, with or without hypertension,	332	Valsartan v/s Amlodipine	80mg v/s 5mg	percent change in Elevated urine albumin excretion (UAER)	Valsartan superior to Amlodipine
IDNT	Prospective randomized double-blind placebo controlled	Type 2 diabetic patients with nephropathy	1715	Irbesartan Amlodipine	75-150 mg 2.5-5 mg	Doubling of serum creatinine level, ESRD, or death	ARB superior to placebo
ROADMAP	randomized double-blind placebo-controlled parallel-group multicenter	Type 2 diabetic patients	4449	olmesartan	40 mg	First onset of microalbuminuria	Olmesartan was associated with a delayed onset of microalbuminuria superior to placebo
Yayoi Nishida et al	Retrospective Data base study	mild to moderate hypertension	6,724 11,069	Olmesartan Candesartan	5-40 mg 1-12 mg	Potassium, creatinine and urea nitrogen.	Both shows improvement in renal function (small)
Jan Galle et.al	Prospective randomized double-blind multicentre parallel-group	Type 2 diabetes and overt nephropathy	885	telmisartan v/s valsartan	40-80 mg v/s 80-160 mg	24-h urinary protein excretion rate (UPER)	Similar renoprotection by both
AIPRI	multicenter double-blind randomized placebo controlled	Non-diabetic CKD	300 283	Benazepril	10 mg/day	Doubling of serum creatinine level or ESRD	ACEi superior to placebo
REIN	multicenter double-blind randomized placebo controlled	Non-diabetic CKD	352	Ramipril	2.5-5 mg/day	Decline in GFR	ACEi superior to placebo

REFERENCE

1. Mogensen CE. Diabetes and hypertension. Lancet 1979; 1: 388–389
2. Parving HH, et al. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet 1983; 1: 1175–1179
3. Jafar TH, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001; 135: 73–87
4. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. A blood pressure-independent effect. Circulation 2002; 106: 672–678
5. Schmid M, et al. Increased genetic risk of hypertension in glomerulonephritis? J Hypertens 1990; 8: 573-577
6. Fagerudd JA, et al. Predisposition to essential hypertension and development of diabetic nephropathy in IDDM patients. Diabetes 1998; 47: 439-444.
7. Strojek K, et al. Nephropathy of type II diabetes: evidence for hereditary factors? Kidney Int 1997; 51: 1602-1607
8. Flack JM, et.al Prevention of hypertension and its complications: theoretical basis and guidelines for treatment. J Am Soc Nephrol 2003; 14 Suppl 2: S92-98.
9. Levey AS. Nondiabetic kidney disease. N Engl J Med 2002; 347: 1505-11511.
10. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160: 685-693.
11. Maki DD, et.al Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995; 155: 1073-1080.
12. Kasiske BL, et.al Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 1993; 118: 129-138.
13. Jafar TH, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001; 135: 73- 87.
14. Masaomi Nangaku, et.al Renoprotection with Anti-Hypertensives: Reduction of Proteinuria and Improvement of Oxygenation via Inhibition of the Renin-Angiotensin System Current Hypertension Reviews, 2005, 1, 67-76 67
15. Taal MT, Brenner BM. Renoprotective benefits of RAS inhibition: From ACEI to angiotensin II antagonists. Kidney Int 2000; 57: 1803-1817.
16. Remuzzi G, et.al. Chronic renal diseases: Renoprotective benefits of renin-angiotensin system inhibition. Ann Intern Med 2002; 136: 604-615.
17. Bidani AK, et.al Lack of evidence of blood pressure-independent protection by renin-angiotensin system blockade after renal ablation. Kidney Int 2000; 57: 1651-1661.
18. Griffin KA, et.al Renoprotection by ACE inhibition or aldosterone blockade is blood pressure dependent. Hypertension 2003; 41: 201-206.
19. American Diabetes Association: Standards of medical care in diabetes—2011. Diabetes Care 34 (Suppl. 1):S11–S61, 2011
20. Remuzzi G, Macia M, Ruggenenti P: Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. J Am Soc Nephrol 17:S90–S97, 2006
21. Lewis EJ, et.al Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860, 2001
22. Brenner BM, et.al SRENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
23. Agarwal R. Proinflammatory effects of oxidative stress in chronic kidney disease: role of additional angiotensin II blockade. Am J Physiol Renal Physiol 2003; 284: F863-869.
24. Nangaku M, Miyata T, Sada T, et al. Anti-hypertensive agents inhibit in vivo the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model. J Am Soc Nephrol 2003; 14: 1212-1222
25. Miyata T, et al. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. J Am Soc Nephrol 2002; 13: 2478-2487
26. Martins D, et.al The epidemiology of end-stage renal disease among African-Americans. Am J Med Sci 2002; 323: 65-71
27. Muirhead N. The rationale for early management of chronic renal insufficiency. Nephrol Dial Transplant 2001; 16 Suppl 7: 51-56.