Dual blockade of the renin-angiotensin-aldosterone system is safe and effective in reducing albuminuria in Asian type 2 diabetic patients with nephropathy

Tan F, Mukherjee J J, Lee K O, Lim P, Liew C F

ABSTRACT

Introduction: Blockade of the renin-angiotensin-aldosterone system (RAAS) by either the angiotensin converting enzyme inhibitor (ACE-I) or the angiotensin II receptor blocker (ARB) has been shown to reduce albuminuria and delay the progression of diabetic nephropathy. This study evaluated the effect of dual blockade of the RAAS by adding an ACEI or an ARB to the administration of either drug alone on albuminuria in Asian type 2 diabetic patients with nephropathy.

Methods: 34 patients were randomly assigned to receive either enalapril 20 mg or losartan 100 mg once daily for eight weeks. Following this, all patients received a combination of enalapril 10 mg and losartan 50 mg daily for eight weeks, followed by enalapril 20 mg and losartan 100 mg daily for another eight weeks. The blood pressure and 24-hour urinary albumin excretion (UAE) were monitored.

Results: Following monotherapy with enalapril, there was a mean and standard error (SE) reduction in the UAE and mean arterial pressure (MAP) of 9.8 (SE 6.8) percent (p-value is 0.061) and 5.3 (SE 2.2) mmHg (p-value is 0.026), respectively; the reduction in UAE and MAP following monotherapy with losartan was by 10.9 (SE 14.1) percent (p-value is 0.053) and 4.5 (SE 1.9) mmHg (p-value is 0.034), respectively. Combination therapy with enalapril and losartan further reduced the UAE (11.2 [SE 8.7] percent, p-value is 0.009] despite there being no significant change in the MAP (−1.2 [SE 1.47] mmHg, p-value is 0.42). The adverse effects included dry cough (seven [19.4 percent] patients, resulting in the withdrawal of medication in two patients), and transient hyperkalaemia (two [six percent] patients).

Conclusion: Dual blockade of the RAAS is safe and effective in reducing albuminuria in Asian type 2 diabetic patients with nephropathy.

Keywords: ACE inhibitor, albuminuria, angiotensin receptor blocker, diabetic nephropathy, renin-angiotensin system

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INTRODUCTION

Diabetic nephropathy remains a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (DM). It is characterised by persistent albuminuria, hypertension and progressive worsening of renal function. Apart from strict glycaemic control and the aggressive lowering of blood pressure (BP), the blockade of the renin-angiotensin-aldosterone system (RAAS) has been shown to confer significant renal protection in terms of the reduction of albuminuria and the retardation of renal failure. The effects of two such classes of drugs, namely the angiotensin converting enzyme inhibitor (ACE-I) and the angiotensin II type 1 receptor blocker (ARB), have been extensively studied in diabetic nephropathy. ACE-I has been shown to reduce albuminuria and maintain the glomerular filtration rate in patients with type 1 DM,[1,2] and similar favourable effects have been shown in smaller studies with type 2 DM patients.[3,4] Recently, ARB has been shown to have a comparable anti-proteinuric effect to ACE-I, and large clinical trials have confirmed its renal protective effect in type 2 diabetic nephropathy.[5,6]

The activation of RAAS leads to the formation of angiotensin II (Ag II) that mediates progressive renal injury in diabetic nephropathy.[7] Apart from its vasoconstrictive effect leading to deranged intraglomerular haemodynamics, it also has a proliferative effect that leads to increased cell growth, matrix synthesis and progressive glomerular sclerosis. ACE-I inhibits the angiotensin-converting enzyme (ACE), thereby reducing the synthesis of Ag II. In

Department of Medicine, Sarawak General Hospital, Jalan Tun Ahmad Zaidi Adruce, Kuching 93586, Malaysia

Tan F, MRCP
Consultant

Mukherjee JJ, FRCP
Senior Consultant

Lee KO, FRCP
Senior Consultant and Professor

Lim P, FRCP
Senior Consultant and Professor

Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074

Liew CF, MRCP
Visiting Consultant

Correspondence to:
Dr Florence Tan
Tel: (60) 082 276666
Fax: (60) 082 276734
Email: ftanhs@yahoo.co.uk

addition, it inhibits the degradation of bradykinin, a vasodilator that stimulates nitric oxide, prostaglandin E2, prostacyclin and cyclic guanosine monophosphate production. This might confer additional renal protection, beyond that achieved by the inhibition of Ag II. However, with prolonged ACE-I therapy, the Ag II level can increase through an escape mechanism via peripheral chymase action.[8,9] ARB, on the other hand, acts directly on the Ag II type 1 receptor (AT 1) and thus blocks all the known actions of Ag II. In addition, by blocking AT 1, it provides unopposed stimulation of the Ag II type 2 receptor (AT 2) in the kidney. Stimulation of the AT 2 receptor has been associated with increased nitric oxide production, increased natriuresis as well as growth inhibitory effects.[7] In order to take advantage of the distinct properties of both these medications, a number of studies have explored the possibility of dual blockade of the RAAS with ACE-I and ARB. While some studies have reported a superior anti-proteinuric effect with combination therapy,[10-14] others have reported no such additional benefit.[15-17] A recent meta-analysis by Jennings et al reported a greater reduction in proteinuria with combination therapy when compared with ACE-I alone.[18] The response to treatment with ACE-I and ARB may differ among different races.[19] This study was therefore undertaken to compare the effect of an add-on ACE-I or ARB to the administration of either drug alone on albuminuria in a cohort of Asian type 2 diabetic patients with nephropathy.

METHODS

Adult patients with type 2 DM, diagnosed according to the World Health Organization criteria, were recruited from the diabetic clinic at our hospital if they had albuminuria of more than 300 mg/day, without clinical or laboratory evidence of a urinary tract infection or other renal disease. The exclusion criteria were creatinine clearance of less than 25 ml/min, malignant hypertension, systolic BP < 100 mmHg or > 200 mm Hg, glycosylated haemoglobin (HbA1c) > 10%, serum potassium > 5 mmol/L, a history of cardiovascular event within the last three months, pregnancy or plans for pregnancy, drug or alcohol abuse, a known allergy to ACE-I or ARB, and constant usage of non-steroidal anti-inflammatory drugs.

This was a randomised, open label, prospective study. The patients underwent a four-week washout period, where their ACE-I or ARB was replaced by other antihypertensive medications. During this period, the dosages of their antihypertensive medications were adjusted to attain or maintain a BP < 140/90 mmHg. They were then randomly assigned to receive either enalapril (Ranbaxy, Sungai Petani, Kedah, Malaysia) 20 mg or losartan (Merck, Sharp & Dohme Ltd, Cramlington Northumberland, England) 100 mg once daily for eight weeks. Following this, all patients received a combination of enalapril 10 mg and losartan 50 mg once daily for eight weeks, followed by enalapril 20 mg and losartan 100 mg once daily for another eight weeks. The patients attended the clinic for a total of five times: screening visit, beginning of each treatment period at Weeks 0, 8 and 16, and at the end of the study period at 24 weeks. At each clinic visit, a study nurse measured their BP twice in a sitting position after ten minutes of rest, with a standard mercury sphygmomanometer using Korotkoff phase one for systolic BP and phase five for diastolic BP. The measurements were taken ten minutes apart, and both the mean BP readings were calculated and recorded. The mean arterial pressure (MAP) was expressed as the sum of one-third of the systolic and two-thirds of the diastolic BP.

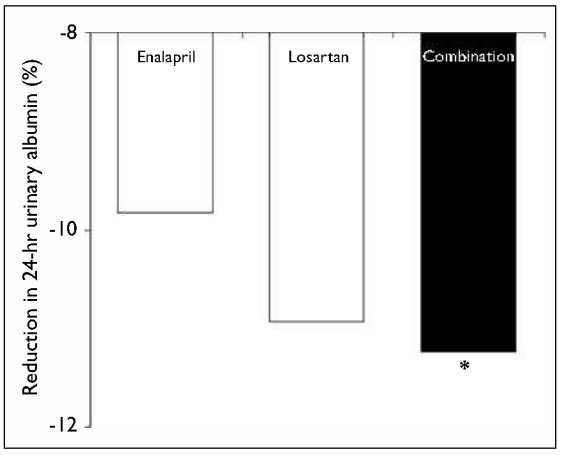

Fig. 1 Percentage reduction in 24-hour urinary albumin during Enalapril, Losartan and combination therapy.
* denotes significant reduction from baseline (P = 0.009).

The urinary albumin excretion (UAE) and creatinine clearance were determined from a timed 24-hour urine collection. HbA1c (high performance liquid chromatography variant) (Bio-Rad, Hercules, CA, USA), serum electrolytes, urea, creatinine and the serum lipid profile (standard method) were measured from a fasting venous blood sample at each visit. The study was approved by the local institutional ethics committee, and all patients provided their written informed consent before participating in the study.

This study had an 80% power to detect a 10% reduction in albuminuria, with a sample size of 16 patients, assuming a baseline albuminuria of three and standard deviation (SD) of 0.3 in log scale (á = 0.05). UAE was expressed as albuminuria at the end of each treatment period. Values for albuminuria were log-

Table I. Baseline characteristics of the patients.

Characteristic	Overall (n = 34)	ACE-I (n = 16)	ARB (n = 18)	p-value
Age (years)	58.2 ± 9.6	58.9 ± 8.9	57.56 ± 10.3	0.68
Duration of DM (years)	13.5 ± 7.5	12.8 ± 7.9	14.2 ± 7.4	0.60
No. of Female (%)	9 (26)	4 (25)	5 (28)	0.86
Systolic BP (mmHg)	143.8 ± 15.2	142.5 ± 14.6	144.9 ± 16.0	0.64
Diastolic BP (mmHg)	83.0 ± 8.4	83.2 ± 7.8	82.8 ± 9.1	0.89
HbA1c (%)	8.0 ± 1.2	7.9 ± 1.1	8.0 ± 1.2	0.91
Creatinine clearance (ml/min)	59.5 ± 24.6	62.9 ± 26.4	56.4 ± 23.3	0.45
Albuminuria (mg/day)	1431.9 ± 1423.0	1446.5 ± 1450.3	1418.8 ± 1440.2	0.96

Data are expressed as mean ± SD.
ARB: angiotensin receptor blocker; ACE-I: angiotensin converting enzyme inhibitor; DM: diabetes mellitus; BP: blood pressure

transformed and expressed as mean ± standard error (SE) to correct for skewing in the distribution, while normal distributed variables are expressed as mean ± SD, unless otherwise stated. The reduction in the MAP and UAE are expressed as absolute reduction and percentage change for each treatment period, respectively. All analyses were performed using the Statistical Package for the Social Sciences version 10.0 (SPSS, Chicago, IL, USA). All data is compared using the paired student's *t*-test, and $P < 0.05$ was considered to be statistically significant (two-tailed test).

RESULTS

Of the 54 patients screened, 36 met the inclusion and exclusion criteria. Two (5.6%) patients were withdrawn from the study before the eighth week due to an intolerable cough induced by enalapril. In total, 34 patients (nine female) completed the study. There were 22 (64.7%) Chinese, ten (29.4%) Malay and two (5.9%) Indian patients. The mean known duration of DM was 13.5 years. One patient was on diet control alone, 18 (53%) were on oral hypoglycaemic agents and 15 (44%) were on insulin treatment. 30 (88%) patients were hypertensive, of whom 60% were on more than two antihypertensive agents for BP control. There was no significant difference in the baseline characteristics between the group assigned to enalapril and the group assigned to losartan (Table I).

There was a mean ± SE reduction in the MAP of 5.3 ± 2.2 mmHg (p = 0.026) and a UAE of 9.8% ± 6.8% (p = 0.061) in the group receiving enalapril 20 mg once daily. The MAP reduction was 4.5 ± 1.9 mmHg (p = 0.034) in the group receiving losartan 100 mg once daily. The reduction in UAE was 10.9% ± 14.1% (p = 0.053) in this group. There was no statistically significant change in HbA1c (Table II).

Combination therapy resulted in a significant reduction in albuminuria (11.2 ± 8.7%, p = 0.009) (Fig. 1) when compared to monotherapy, despite there being no significant change in MAP (–1.2 ± 1.47 mmHg, p = 0.42). A low-dose combination therapy (enalapril 10 mg plus losartan 50 mg daily) further significantly reduced albuminuria when compared to that achieved by using either agent alone. Despite the existence of a trend, there was no statistically significant further reduction of albuminuria on doubling the doses of enalapril and losartan during combination therapy, compared to that achieved with a low-dose combination therapy (Table II).

The most common adverse event was a dry cough, which occurred in seven (19.4%) patients, four during enalapril monotherapy and three during the combination therapy period. Most were mild and intermittent, but in two patients, it was severe enough to result in a withdrawal from the study. Hyperkalaemia (potassium > 5.5 mmol/L) occurred in two (6.0%) patients, both during combination treatment with ACE-I and ARB. Both episodes of hyperkalaemia were transient and did not necessitate the cessation of therapy. There was a mild but significant reduction in creatinine clearance in the group that was treated with losartan (6.4 ml/min drop [2.0–10.7], p = 0.007). HbA1c and the lipid profile did not change significantly throughout the study period in both groups.

DISCUSSION

Similar to previous studies,[20,21] this study showed the comparable and beneficial effects of ACE-I monotherapy and ARB monotherapy in lowering BP and reducing albuminuria in type 2 DM patients with clinical nephropathy. With the optimal recommended doses of enalapril or losartan monotherapy, the effect of dual blockade of the RAAS using combination therapy with ARB and ACE-I was then examined. The study showed that combination therapy leads to a further reduction in albuminuria despite minimal changes in the mean BP.

ACE-I has traditionally been the treatment of choice for diabetic nephropathy, based on earlier studies in type 1 diabetic patients with nephropathy.[1,2] With

Table II. Blood pressure (BP) and albuminuria before and after enalapril, losartan and combination therapy.

	Monotherapy						Combination Therapy					
	ACE-I			ARB			Low dose			High dose		
	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value
Mean BP ± SE (mmHg)	103.0 ± 2.2	97.7 ± 1.7	0.026	103.5 ± 2.1	99.0 ± 2.1	0.034	98.4 ± 1.35	96.7 ± 1.58	0.217	96.7 ± 1.58	99.6 ± 1.68	0.059
Albuminuria ± SE (mg/day)	1,447 ± 363	1,237 ± 316	0.061	1,419 ± 339	1,114 ± 298	0.053	1,172 ± 214	1,027 ± 200	0.016	1,027 ± 200	970 ± 201	0.332

ARB: angiotensin receptor blocker; ACE-I: angiotensin converting enzyme inhibitor: SE: standard error

the introduction of ARB, large trials involving type 2 diabetic patients have confirmed its renal protective effects in terms of the normalisation of microalbuminuria and retardation of the progression of DM nephropathy, and in delaying the onset of end-stage renal failure (ESRF) or in doubling serum creatinine.[5,6] Prolonged ACE inhibition has been associated with "ACE-escape" due to the production of Ag II through the ACE independent pathway.[8,9] In recent years, there has been great interest in the dual blockade of the RAAS to confer additive renal and cardiac protection. Mogensen et al studied 197 hypertensive patients with type 2 DM and microproteinuria, and found that combination therapy with once daily candesartan 16 mg and lisinopril 20 mg was more effective in reducing BP and albuminuria than monotherapy with either drug alone.[12] However, as the reduction of BP was 8 mm Hg greater with combination therapy than with monotherapy, it is not known whether the further reduction in albuminuria seen in this study was merely secondary to more effective BP lowering. Similarly, Cetinkaya et al found that a combination of enalapril 10 mg daily and losartan 50 mg daily decreased both the proteinuria and MAP by a greater extent when compared with the administration of either drug alone.[13] In two separate randomised double-blind crossover studies, Rossing et al found a further reduction in albuminuria when candesartan 16 mg was added to the pre-existing ACE-I therapy in hypertensive type 2 diabetic patients. In the first study involving 18 type 2 diabetic patients who were taking the recommended doses of ACE-I, corresponding to 20 mg of enalapril/lisinopril once daily or 100 mg of captopril daily, the administration of candesartan 16 mg daily for two months induced a 25% reduction in albuminuria, together with a 10 mmHg reduction in 24-hour systolic BP.[10] In the second study involving 20 type 2 diabetic patients on a maximal recommended dose of ACE-I (enalapril/lisinopril 40 mg daily or captopril 150 mg daily), there was a further 28% significant reduction in albuminuria, and a modest but non-significant reduction in BP after two months of being administered candesartan at 16 mg daily.[11]

On the other hand, the addition of Losartan 50 mg daily for one month did not improve proteinuria in 16 obese, hypertensive patients (12 with diabetic nephropathy) with moderately advanced renal failure and heavy proteinuria (mean urinary protein 3.8 g/day).[15] A Korean group also reported no beneficial effect on proteinuria when candesartan was added to ramipril therapy in type 2 diabetic patients with nephropathy despite the positive anti-proteinuric effect seen in patients with IgA nephropathy following the same regimen.[16,17]

The present study showed that when compared to monotherapy with either ACE-I or ARB, combination therapy resulted in a significant further reduction in albuminuria in Asian type 2 diabetic patients. This additional anti-albuminuric effect of combination therapy was seen even at half maximal doses of enalapril and losartan. Two previous studies have shown similar findings. In both these studies, combination therapy using half maximal doses of ACE-I and ARB was more effective in reducing albuminuria and urinary transforming growth factor beta in patients with diabetic nephropathy when compared to using full doses of ACE-I and ARB alone.[22,23] However, the authors of both these studies did not examine the effect of a higher-dose combination therapy. Interestingly, in our study, although combination therapy with half maximal doses of ACE-I and ARB showed a significantly greater reduction in albuminuria compared to using full doses of either agent alone, doubling the dose of ACE-I and ARB during combination therapy only showed a non-significant trend in the further reduction of albuminuria. Further studies are needed to confirm this observation and to determine the optimal combination dose to use in order to maximise the anti-albuminuric effect while minimising potential risks and side effects.

The additional anti-albuminuric effect of combination therapy in this study was seen despite there being no significant further drop in BP during

combination therapy. This BP-independent anti-proteinuric effect of the RAAS blockade has also been shown in previous studies.[10,12,13] It is postulated that local renal RAAS activity required a higher blockade than systemic RAAS activity responsible for systemic blood pressure. The blockade of local renal RAAS is responsible for a further reduction in the intraglomerular pressure by preferentially dilating the postglomerular arterioles,[24] as well as improving the charge and size selectivity of the glomerular basement membrane.[25]

The two main limitations of this study were the small sample size and the short follow-up period. The small sample size did not allow us to examine the differences in response among the different racial groups. Also, since the effect of combination therapy on urine albumin excretion, a surrogate marker for renal injury, has been studied, it is not possible to determine the long-term efficacy or benefits of combination therapy on renal function from this study. Another limitation was the fact that we did not examine whether a similar anti-albuminuric effect could be achieved by further escalating the doses of ACE-I or ARB during monotherapy. While losartan 100 mg daily is considered to be the optimal effective dose for maximal reduction of proteinuria,[26,27] the optimal dose of enalapril for maximal proteinuria reduction is still unknown. An anti-proteinuric effect above the 20 mg enalapril equivalent has not been studied in large clinical trials,[28] although in nine non-diabetic patients, the further reduction of proteinuria was seen with lisinopril 40 mg daily.[27] It remains unknown if a further increment in the dosage of enalapril would have resulted in a further anti-proteinuric effect. In Asian populations, higher doses of ACE-I might not be well tolerated due to a relatively smaller body size and a greater propensity to ACE-I-induced cough that has been reported to be two- to five-fold higher than in Caucasian patients.[29,30] Cough occurred in 19.4% of our patients, and in two of them, it was severe enough to result in the cessation of therapy. A less common but more serious side effect, hyperkalaemia, developed in two of our patients. The first patient was a 48-year-old man with a baseline creatinine clearance of 36 ml/min. His baseline serum potassium was 4.7 mmol/L, which rose to 5.9 mmol/L during the high-dose combination therapy. The second patient was a 71-year-old man with a baseline creatinine clearance of 50 ml/min. His serum potassium rose from 4.0 mmol/L to 6.3 mmol/L. Although both episodes of hyperkalaemia were transient and did not lead to the discontinuation of therapy, this important side effect should be monitored carefully, especially in the elderly and in patients with underlying renal impairment.

In conclusion, this study has shown that dual blockade of the RAAS with ACE-I and ARB is safe and effective in reducing albuminuria in Asian type 2 diabetic patients. Dual blockade using half the maximal recommended doses for ACE-I and ARB resulted in a significant further reduction in albuminuria when compared to using either agent alone, with no significant further reduction in albuminuria on doubling the doses of ACE-I and ARB during combination therapy. Further studies are required to determine the optimal combination doses of ACE-I and ARB so as to maximise the benefit with minimal risk, and to examine the long-term effects of such an optimal combination therapy causing dual blockade of the RAAS on renal function and mortality.

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