Transforming growth factor β1 and additional renoprotective effect of combination ACE inhibitor and angiotensin II receptor blocker in hypertensive subjects with minor renal abnormalities: a 24-week randomized controlled trial

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Objective To verify the benefit of renin–angiotensin system blockade in hypertension, the effects of 24 weeks' losartan and ramipril treatment, both alone and in combination, on urinary albumin excretion (UAE) and circulating transforming growth factor β1 (TGFβ1) have been evaluated in hypertensive subjects with minor renal abnormalities.

Design and methods Fifty-one patients with stage 1 and 2 essential hypertension and with UAE ≥20 mg/24 h but with maintained renal function have been included. After a 4-week run-in with placebo administration, a randomized double-blind, three-arm double-dummy trial was used. All the hypertensives (HT) were allocated randomly to three treatment arms (17 patients for each group) and they were single-matched for age, gender, body mass index (BMI), systolic and diastolic blood pressure. Active treatment consisted of losartan (50 mg/day), ramipril (5 mg/day) and combined (losartan 50 mg/day plus ramipril 5 mg/day) for 24 weeks. Hydrochlorothiazide 12.5 mg/day was added in HT patients with uncontrolled blood pressure (≥140/90 mmHg) during the active treatment period. In all patients UAE, by immunonephelometric assay; circulating TGFβ1 by a solid-phase specific sandwich enzyme-linked immunosorbent assay (ELISA); and blood urea nitrogen (BUN), creatinine and creatinine clearance and potassium, by routine laboratory methods, were determined after placebo treatment and 24 weeks follow-up.

Results The three treatment groups were comparable for gender, age, BMI, blood pressure, UAE and renal function measurements. During the active treatment period it was necessary to add hydrochlorothiazide in five patients – two each of the losartan and ramipril groups and one of the combined group. At the end of treatment, significant ($P < 0.05$) reductions in systolic, diastolic and mean blood pressure, UAE and TGFβ1 levels were observed in all the groups. No change in renal function measurements were observed. The absolute and percentage reduction in UAE and TGFβ1 were significantly higher in the combined group than in the losartan or ramipril groups. No significant changes in absolute and percentage reduction of systolic, diastolic and mean blood pressure were found. All treatment regimens were well tolerated with few and transient side-effects.

Conclusion These data indicate an additional renoprotective effect of dual blockade of the renin–angiotensin system (RAS) in hypertensive patients with minor renal abnormalities. In addition, the contemporaneus and marked decrease in TGFβ1 and UAE levels in hypertensives treated with combined therapy might indicate the presence of a subset of subjects who may benefit from complete RAS blockade. *J Hypertens* 23:657–664 © 2005 Lippincott Williams & Wilkins.

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Introduction

At present, renoprotection represents one of the most important goals of antihypertensive treatment [1]. Accordingly, recent guidelines of European Society of Hypertension and European Society of Cardiology [2] have recognized the relevance of minor abnormalities of renal function for the stratification of hypertensive patients. In addition, it has been proposed that screening for microalbuminuria in the general population could be a tool to detect subjects at risk for progressive renal failure, since glomerular hyperfiltration and microalbuminuria have to be considered markers of later development of renal failure in diabetic and non-diabetic patients [3]. Progressive accumulation of extracellular matrix is a main

cause of renal impairment in both animals and humans [4]. Accordingly, overproduction of the cytokine transforming growth factor β1 (TGFβ1) has been reported to play a key role in renal fibrosis. In particular, increased synthesis of collagens, fibronectin and proteoglycans, decreased degradation of matrix proteins, and increased synthesis and expression of a group of cell matrix receptors, called integrins, which enhance local matrix deposition, have been attributed to TGFβ1 overproduction [5]. Furthermore, Kopp *et al.* [6] reported that transgenic mice with high circulating TGFβ1 develop severe progressive kidney fibrosis and die from renal failure.

Several factors known to be injurious to the kidney have been found to increase TGFβ1 expression and, among these, a relevant role has been attributed to angiotensin II (ANG II). Some recent experimental studies have demonstrated that ANG II blockade results in a decrease in TGFβ1 expression and matrix accumulation, suggesting that its antifibrotic effect may be mediated through a reduction of this cytokine [7,8].

Drugs that block the actions of ANG II have shown beneficial effects in experimental kidney diseases and in human hypertension. In fact, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II type receptor blockers (ARB) have been found to preserve renal function in various clinical conditions [9–12]. These favourable effects occur through an evident reduction in proteinuria and glomerular hypertension, able to prevent development of kidney fibrosis [13]. Both classes of agents inhibit the vasoconstrictive effects of angiotensin II at the efferent arteriole, either by reducing the concentration of angiotensin II or by blocking its receptor [13,14]. This specific site of action explains the better nephroprotective properties attributed to ACEi and ARB than to other antihypertensive drugs. Clinical data comparing ACEi and ARB therapy in renal disease are often limited to short-term studies, which indicate that ARB have equivalent effects to ACEi on the determinants of renal disease progression, specifically blood pressure and proteinuria [15,16]. Other data suggest that combination therapy with ACEi and ARB may offer a better therapeutic effect than treatment with either agent alone [17,18]. Although systemic or glomerular hypertension are important factors in renal injury, some data indicate that the therapeutic effect of ANG II blockade is partially independent due to its haemodynamic effects [19–21]. In particular, the ANG II blockade significantly slows the progression of renal failure even in the absence of increased blood pressure [22]. In these cases, ANG II blockade-mediated improvement in endothelial function and reduction in TGFβ1 levels have been reported to ameliorate renal function. In addition, a reduction of circulating TGFβ1 after administration of ACEi or ARB, alone or in combination, has been reported recently in subjects with diabetic nephropathy [21–24].

Although a combination of ACEi and ARB treatment seems attractive, thus far limited data have emerged to support such a strategy. Few clinical studies have been designed to evaluate the role of the link between TGFβ1 overproduction and human hypertensive nephropathy, and the role of its reduction as a nephroprotective target of antihypertensive therapy [23]. Accordingly, the aim of the present study was to determine the effect of 24 weeks' losartan and ramipril administration on TGFβ1 circulating levels and urinary albumin excretion in hypertensive subjects. The main goal of the study was to evaluate whether circulating TGFβ1 overproduction may be a marker for detection of hypertensive patients who may particularly benefit from renin–angiotensin-system blockade. For this reason, hypertensive subjects with minor renal abnormalities were allocated randomly to 24 weeks of treatment with ACEi or ARB alone or in combination.

Patients and methods

Patients

Subjects eligible for the study were screened for arterial hypertension at the antihypertensive centre of the Department of Internal Medicine, University of Palermo, Italy. Subjects with a casual systolic blood pressure (SBP) $\geq$140 mmHg and <180 mmHg and/or with casual diastolic blood pressure (DBP) $\geq$90 mmHg and <110 mmHg, obtained with a standard sphygmomanometer after 5 min of rest on three independent occasions, were invited to our day hospital for a detailed medical examination, including history taking, physical examination, routine laboratory examination and 24-h urine sampling. Ultrasonography of the kidneys and duplex sonography of the renal arteries were performed where indicated. Inclusion criteria were: stage 1 and 2 essential hypertension, urinary albumin excretion (UAE) $\geq$0.02 g/24 h ($\geq$20 mg/24 h) with maintained renal function (serum creatinine concentration <1.30 mg% in women and <1.40 mg% in men), according to the guidelines of the European Society of Hypertension and European Society of Cardiology [2]. Exclusion criteria included the presence of any form of secondary hypertension, stage III essential hypertension, any irreversible and organ damage due to arterial hypertension, left ventricular hypertrophy, cardiovascular disease, diabetes, dyslipidaemia, hepatic disease, malignant disease. In all hypertensives, M- and B-mode echocardiography was performed to assess left ventricular hypertrophy (LVH). Accordingly, all the patients with indexed left ventricular mass (LVM/height$^{2.7}$) $\geq$ 50 g/m$^{2.7}$ for men and $\geq$ 47 g/m$^{2.7}$ for women [24] were considered to have LVH and were excluded from the study. The mean value for LVM/height$^{2.7}$ was 41 ± 5, 40 ± 4 and 40 ± 5 g/m$^{2.7}$, respectively, in losartan, ramipril and combined treatment groups. Accordingly, from a large number of hypertensives, we established three groups of patients, single-matched for age, gender, body mass index (BMI),

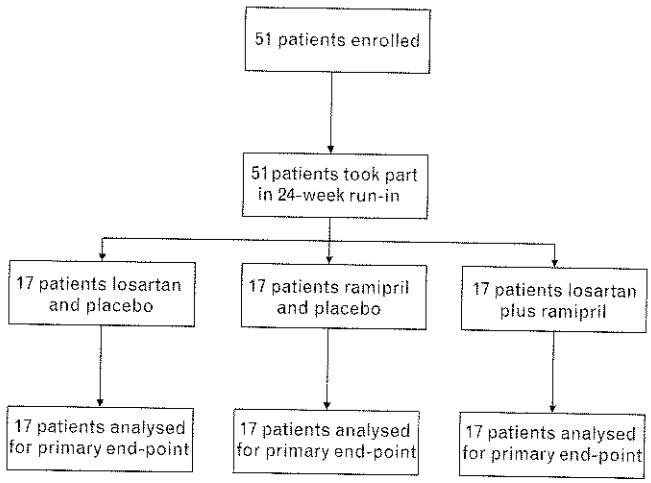
SBP and DBP. Fifty-one patients fullfilled the selection criteria, and baseline characteristics of the study participants are given in Table 1.

Study design and active treatment

Each patient gave written consent after receiving a detailed description of the study procedure. The study was approved by the ethics commitee of our institution. Multiple comparisons power analysis was performed to determine sample size. The primary end-point was considered to be the level of TGFβ changes, and sample size was computed based on the following assumptions: $\alpha = 0.05$, power of at least 0.80 (β error equal or below 0.20), a minimum detectable difference of 3.00 with a standard deviation of 2.00 (minimum detectable difference/standard deviation = 1.5). The total sample size was 51 subjects (17 subjects for each of the three arms); it achieved 83% power using the Hsu (With Best) multiple comparison test at 0.05000 significance level.

This study was a randomized, double-blind, three-arm double-dummy trial. It was planned and conducted according to the revised recommendations for improving the quality of report or randomized trials [25]. We studied three groups of subjects, each of them matched for age, BMI and blood pressure values. Then groups were allocated randomly into one of the three therapy arms. The first arm was treated with losartan 50 mg/day, the second arm was treated with ramipril 5 mg/day and the third was treated with a combination of the two drugs (losartan 50 mg/day plus ramipril 5 mg/day) (Fig. 1). Blood pressure normalization (SBP $\leq$ 140 mmHg and DBP $\leq$ 90 mmHg) occurred in all hypertensives. To achieve this goal, a couple of patients in each treatment group also received hydrochlorothiazide (12.5 mg once daily) (losartan group: $n = 2$ patients; ramipril group: $n = 2$ patients; combined group: $n = 1$ patient). The follow-up was 24 weeks.

Fig. 1



Trial profile.

Each patient entered into the study was uniquely identified for study purposes by a four-digit patient number, and each group was labelled by a letter corresponding to a drug regimen that was concealed until statistical analysis was complete. The drug regimen was double-dummy, so each group received two tablets (one pharmacologically active plus placebo, except the group that received two pharmacologically active drugs). Both placebo and active drug tablets were indistinguishable but for a letter label. Severe adverse reactions were monitored to enable the study to be stopped early if they emerged. The patient code was revealed to the clinical researchers once recruitment, data collection, laboratory analyses and statistical analysis were completed. No patient dropped out from the study, so all data of all patients were collected and analysed. An independent biostatistics expert analysed data and performed inferential analysis. All data analysis

Table 1 Effects of treatments on blood pressure, urinary albumin excretion renal function measurements and TGFβ1

Cases	Losartan $n = 17$		Ramipril $n = 17$		Combined $n = 17$	
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
Sex (F/M)	9/8	9/8	9/8	9/8	9/8	9/8
Age (years)	56 ± 7	56 ± 7	54 ± 9	54 ± 9	58 ± 7	58 ± 7
BMI (kg/m^2)	31.7 ± 4.4	31.8 ± 4.5	29.5 ± 4.5	29.1 ± 4.2	30 ± 4.9	29.7 ± 4.6
SBP (mmHg)	163 ± 10	133 ± 6*	159 ± 12	134 ± 5*	162 ± 9	130 ± 6*
DBP (mmHg)	93 ± 8	82 ± 6*	98 ± 7	80 ± 8*	93 ± 9	77 ± 6*
MBP(mmHg)	116 ± 8	100 ± 7*	118 ± 9	99 ± 8*	116 ± 10	95 ± 7*
UAE (g/24 h)	0.35 ± 0.24	0.21 ± 0.11*	0.44 ± 0.31	0.33 ± 0.17*	0.46 ± 0.32	0.22 ± 0.21*
BUN(mg/dl)	42 ± 9	42 ± 8	37 ± 9	38 ± 6	42 ± 11	43 ± 10
Creatinine (mg/dl)	1.05 ± 0.2	1.09 ± 0.2	1.02 ± 0.1	1.03 ± 0.2	1.02 ± 0.2	1.06 ± 0.2
Creatinine Clearance	70 ± 14	69 ± 17	73 ± 17	75 ± 16	70 ± 17	67 ± 15
Serum potassium	4.7 ± 0.5	4.7 ± 0.7	4.5 ± 0.6	4.7 ± 0.8	4.6 ± 0.6	4.8 ± 0.7
TGFβ1 (ng/ml)	6.3 ± 4.3	2.9 ± 2*	5.6 ± 3.1	3.2 ± 2.4*	7.2 ± 3.6	1.2 ± 0.4*
Minimum	2.4	0.88	1.44	0.93	2.4	0.51
Maximum	19.3	8.4	12	11.6	14.3	2.1
Median	5	2.9	4.67	2.9	6	1.12

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BUN, blood urea nitrogen; UAE: urinary albumin excretion; TGFβ1, transforming growth factor β1. *$P < 0.05$ versus baseline.

was carried out according to a pre-established analysis plan.

The patients attended the clinic for a total of eight study visits: at 4 and 2 weeks before randomization, at randomization (week 0), and at 1, 6, 12, 18 and 24 weeks after randomization. At each visit blood pressure was measured in the morning after 5 min of rest, about 24 h after the previous drug administration. Sitting blood pressure was measured three times with an interval of about 2 min, and the mean was calculated. Mean blood pressure (MBP) was calculated by the formula: DBP plus 1/3 of pulse pressure. At 0 and 24 weeks after randomization urinary albumin excretion and circulating TGFβ1 were determined.

Measurements

Patients underwent a general analytical laboratory parameters profile, including BUN, creatinine and creatinine clearance, glycaemia, electrolytes (serum sodium, potassium, chloride), by routine laboratory methods.

Urinary albumin excretion

To eliminate the intra-individual day-to-day variability of UAE, three consecutive 24-h urine collections were used. In addition, to assess the completeness of a 24-h urine collection, measurements of the urinary rate of clearance of creatinine were evaluated. UAE was measured by immunonephelometric assay (Boehring Institute, Germany; limit of detection, 0.1 mg/dl; inter-assay coefficient 3.5%). Microalbuminuria was defined as a level of UAE $\geq$20 and <300 mg/24 h.

TGFβ1

Blood samples were drawn by venepuncture with care to minimize degranulation of the platelets and to avoid the release of TGFβ1. Peripheral venous blood was obtained from each patient and the sera were isolated and stored at −70°C. Transforming growth factor β1 levels were determined by using a solid-phase specific sandwich ELISA technique (R&D Systems, Inc. Minneapolis, Minnesota, USA) as described previously [26]. The interassay and intra-assay variations for determining TGFβ1 were 8 and 6%, respectively. The sensitivity, hence minimum level of detection of TGFβ1 by sandwich ELISA, was 5 pg/ml.

Statistical analysis

Data are expressed as mean value ± standard deviation. Non-parametric tests were performed to test the null hypothesis and two-sided values of $P < 0.05$ indicated a statistical significant difference. The Wilcoxon signed ranks test was performed to compare data within groups at baseline and after treatment. Group data, both at baseline and after treatment changes, were compared by the Kruskall–Wallis test, used as a non-parametric alternative to the one-way ANOVA. Pairwise comparisons between groups were performed using the Conover–Inman method if the Kruskall–Wallis had pointed out a significant difference among groups.

Results

No significant differences in baseline age, BMI, SBP, DBP, MBP, UAE, BUN, creatinine, serum potassium, creatinine clearance and TGFβ1 values were observed for the losartan, ramipril and combination groups (Table 1).

Significant ($P < 0.05$) decreases in SBP, DBP, MBP, UAE and TGFβ1 levels were observed in all groups at the end of treatment, compared to baseline values. A mild increase in TGFβ1was observed in one patient of the ramipril group at the end of treatment (11.2 ng/ml versus 10 ng/ml). In all groups, no significant changes in BUN, creatinine, creatinine clearance and serum potassium were found at the end of treatment. Figures 2 and 3 show the responses of TGFβ1 and UAE values of individuals to the three treatments.

In the combination therapy group a significant increase in the absolute reduction of TGFβ1 ($P < 0.03$ versus losartan; $P < 0.0001$ versus ramipril) and of UAE ($P < 0.05$ versus losartan; $P < 0.001$ versus ramipril) was found. The percentage reduction in TGFβ1 ($P < 0.03$ versus losartan; $P < 0.0001$ versus ramipril) and in UAE ($P < 0.05$ versus losartan; $P < 0.001$ versus ramipril) was also higher in the combination group. No significant changes in absolute and percentage changes in SBP, DBP and MBP were detected between the three groups (Table 2).

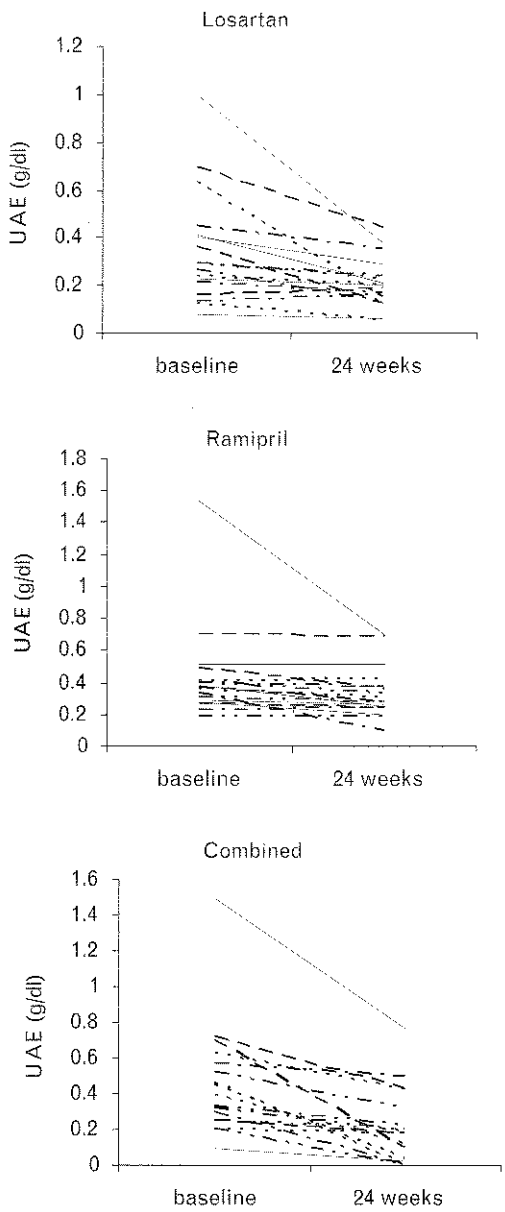
All treatment regimens were generally well tolerated. Side-effects were few and transient. Two patients complained of asthenia, two of cough and three of dizziness, but treatments were not discontinued.

Discussion and conclusions

In the present study we hypothesized that complete inhibition of the renin–angiotensin–aldosterone system (RAS) would be most beneficial in management of progressive hypertensive renal damage, and might be achieved by a dual blockade with ACEi and ARB. To prove this hypothesis we compared the effects of three treatments (monotherapy with ACEi and ARB and its combination) on blood pressure, urinary albumin excretion and TGFβ1 values in hypertensive subjects with minimal renal abnormalities. This was a single-centre trial which, compared with multicentre trials, may have some benefits, such as a simple design, strict implementation and constant analysis of clinical and laboratory data.

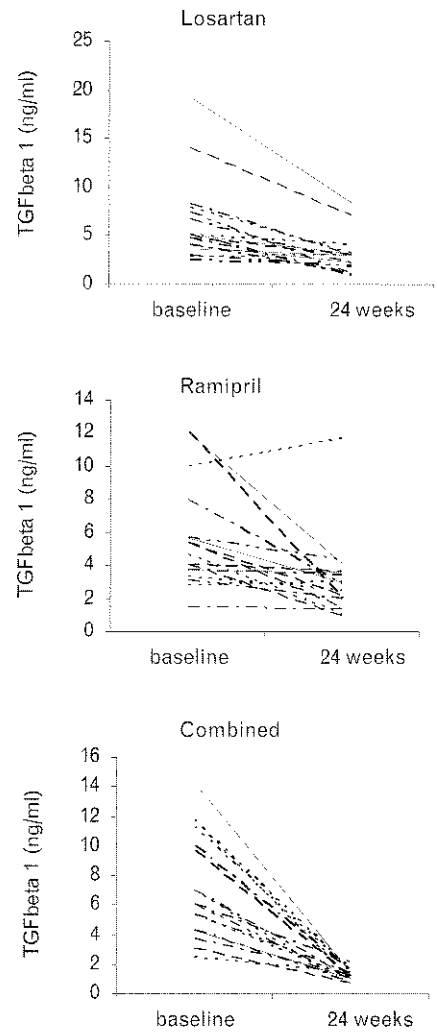
This is the first study designed to analyse the effects of dual RAS blockade on UAE and TGFβ1 in hypertensives with minor renal abnormalities. Our results indicate some interesting findings. First, a more marked antiproteinuric

Fig. 2



Individual responses of urinary albumin excretion (UAE) over the 24 weeks' treatment with losartan, ramipril and the combined treatment.

Fig. 3



Individual responses of transforming growth factor β1 (TGFβ1) over the 24 weeks' treatment with losartan, ramipril and the combined treatment.

effect of the combination of ACEi and ARB than either drug alone has been found in hypertensive subjects with minor renal abnormalities. In fact, treatment with combined therapy reduced UAE by 55% at 6 months, which was significantly superior to UAE reduction obtained with either losartan or ramipril alone. It is important to note that this antiproteinuric effect was obtained with strict blood pressure control in all the groups. This finding discounts the suggestion that the differences observed upon the reduction in UAE could be explained only by the systemic BP effect.

Table 2 Absolute and percent reduction (Д) in transforming growth factor β1 (TGFβ1), urinary albumin excretion (UAE) and blood pressure in the three groups

	Losartan $n = 17$	Ramipril $n = 17$	Combined $n = 17$
Д TGFβ1 (ng/ml)	3.4 ± 2.9	2.4 ± 2.8	$6 \pm 3.4^{*,a}$
Д TGFβ1 (%)	49 ± 26	37 ± 34	$79 \pm 13^{*,a}$
Д UAE (g/24 h)	0.15 ± 0.17	0.11 ± 0.19	$0.25 \pm 0.2^{\bullet,\#}$
Д UAE (%)	31 ± 27	18 ± 21	$55 \pm 32^{\bullet,\#}$
Д SBP (mmHg)	30 ± 8	25 ± 13	32 ± 11
Д SBP (%)	18 ± 4	16 ± 8	19 ± 6
Д DBP (mmHg)	12 ± 10	18 ± 11	17 ± 13
Д DBP (%)	14 ± 9	18 ± 10	17 ± 12
Д MBP (mmHg)	16 ± 9	19 ± 10	22 ± 11
Д MBP (%)	14 ± 7	15 ± 7	18 ± 9

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. Kruskall–Wallis test. $^{*}P < 0.03$ versus losartan. $^{a}P < 0.0001$ versus ramipril. $^{\bullet}P < 0.05$ versus losartan. $^{\#}P < 0.001$ versus rampril.

Secondly, reduction in urinary albumin excretion was associated with a marked decrease in circulating TGFβ1 values. Finally, combined therapy was characterized by an excellent safety profile, and it was supported by maintained renal function and by an inconsistent change in potassium at the end of treatment.

The additive antiproteinuric effect of combined therapy observed here has been found previously in diabetic and non-diabetic kidney disease, but in the latter studies it was related with a greater reduction in blood pressure [27,28].

Both ACEi and ARB now have an established record of effectiveness in the treatment of proteinuric states, renal disease and cardiac heart failure. Although inconclusive, the results of some studies support the notion that additive antihypertensive, cardioprotective and antiproteinuric effects may be obtained with their combined use in certain subsets of patients. Although some authors have reported negative or equivocal data [29,30], others have indicated benefical effects of the combined therapy in diabetic microalbuminuric hypertensive patients [28] and in patients with biopsy-documented IgA nephropathy [31]. In the latter study, a combination of ACEi and ARB produced on average a 73% greater reduction in proteinuria than either agent alone. No further reduction in proteinuria was achieved by doubling the dose of either the ACEi or ARB.

Microalbuminuria is a link between cardiovascular and renal damage in hypertensive diabetic and non-diabetic subjects [32–34]. It represents a renal manifestation of systemic vascular endothelial dysfunction, suggesting a link between increased UAE and an elevated risk for cardiovascular disease [35].

Microalbuminuria is the consequence of two mechanisms: the first is the abnormal transglomerular passage of albumin due to an alteration of the glomerular barrier permeability (involving mainly a loss of restriction to the passage of negatively charged proteins); the second is the subsequently impaired reabsorption by the epithelial cells of the proximal tubuli, particularly by a defect in lysosomal activity [36].

An interesting finding of this study is related to the fact that the reduction in UAE was associated with a marked decrease in circulating TGFβ1. The exact mechanism of this relationship is not entirely known, but recent experimental data have shown that lysosomal activity may be affected by increased TGFβ1 levels [37]. Accordingly, a strong relationship between reduction of the albuminuria excretion rate, increased lysosomal activity and decreased TGFβ1 expression has been reported in diabetic and hypertensive rats treated with ACEi [38]. TGFβ1 is hyperexpressed in human glomerular diseases, including IgA nephropathies [39] and diabetic nephropathy [40]. It has a direct pathogenetic role in elevated blood pressure and increases renin release from juxtaglomerular cells in the kidney [41]. Activation of the renin–angiotensin system is an important feature of progressive renal disease and Ang II stimulates the production of TGFβ1 [8]. Moreover, TGFβ1-neutralizing antibodies block angiotensin II-mediated stimulation of extracellular matrix production in the kidney [42]. The beneficial effect of blocking Ang II production for clinical renal disease have been well demonstrated, and it is likely that these benefits are due, in part, to decreasing TGFβ1 in the kidney. More recent clinical data have demonstrated a relationship between TGFβ1 and progression of hypertensive renal disease [43,44], and a hyperexpression of TGFβ1 in hypertension [45]. Angiotensin II stimulates production of TGFβ1 via the AT1 receptor, and both ACEi and ARB have been demonstrated to reduce production of TGFβ1 in patients with kidney transplants and in those with diabetic nephropathies [23,46].

However, our study has some possible limitations. First, it did not have a placebo group; such a group was not approved by the ethics committee because of the known renoprotection of ACEi. This limitation is unlikely to affect our data because both monotherapies significantly reduced daily UAE. Secondly, we have not assessed the most appropriate dose of each drug in combination treatment. We do not know if a combination of reduced doses of both drugs could offer the same renoprotection as did the dose we used. Doses of losartan and ramipril were equivalent to doses of ACEi and ARB found previously to achieve a maximal reduction in proteinuria [10,47]. In addition, Peters *et al.* [19] reported that submaximal doses of ACEi and ARB in combination are able to induce maximal inhibition of angiotensin II and provide maximal therapeutic efficacy.

Some clinical implications arise from the results of our study. First, combination treatment was well tolerated without evidence of hyperkalaemia after 24 weeks. This provides further evidence to suggest that the present practice of avoiding use of ACEi and ARB or both, to prevent renal impairment and hyperkalaemia, is no longer justified. However, careful observation is still recommended. Secondly, the results of our study support the hypothesis that the protective effects of inhibition of the RAS were associated with the suppression of TGFβ1 production. This might indicate that TGFβ1, in addition to blood pressure, should be a therapeutic target. Higher doses, or different combinations, of drugs that block the RAS, or entirely new drug strategies, may be needed to achieve a greater renoprotective effect.

In view of this, the contemporaneous and marked decrease in TGFβ1 and UAE in the hypertensives treated with combined therapy might indicate that

hypertensive subjects with high baseline circulating TGFβ1 levels may be considered a particular subset of subjects who may particularly benefit from complete RAS blockade.

This conclusion agrees with recent data indicating that serial measurements of TGFβ1 might be useful to provide predictive information on the progression of renal function impairment, and to give an index of the therapeutic efficacy of RAS inhibition in preserving renal function [48]. Therefore, the routine determination of circulating TGFβ1 levels might also be useful in improving the therapeutic strategy for microalbuminuric or proteinuric hypertensive subjects. This approach might also improve the cost-effectiveness ratio. However, the case has to be further supported by data from long-term multicentre trials with appropriate economical analysis.

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