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ORIGINAL ARTICLE

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Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese Losartan Therapy Intended for Global Renal Protection in Hypertensive Patients (JLIGHT) Study

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Abstract

Background. Insufficiency of renal function and high blood pressure influence each other and eventually result in life-threatening endstage renal disease. It has been proposed that proteinuria per se is a determinant of the progression of chronic kidney disease (CKD). The therapeutic strategy for patients with proteinuric CKD and hypertension should therefore be targeted with a view not merely toward blood pressure reduction but also toward renoprotection.

Methods. We examined the effect of the angiotensin $(AT)_1$ receptor antagonist losartan and the calcium channel blocker amlodipine, throughout a period of 12 months, on reduction of blood pressure and renoprotection. This was done by assessing amounts of urinary protein excretion, serum creatinine (SCr), and creatinine clearance (CCr) in patients with hypertension (systolic blood pressure [SBP] $\geqq$ 140 mmHg or diastolic blood pressure [DBP] $\geqq$ 90 mmHg) and CKD (male, body weight [BW] $\geqq$ 60 kg: 1.5 $\leqq$ SCr $<$ 3.0 mg/dl; female or male BW $<$ 60 kg: 1.3 $\leqq$ SCr $<$ 3.0 mg/dl), manifesting proteinuria of 0.5 g or more/day. Losartan was administered once daily at doses of 25 to 100 mg/day, and amlodipine was given once daily at 2.5 to 5 mg/day. No

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antihypertensive combination therapy was allowed during the first 3-month period.

Results. A 3-month interim analysis revealed that, despite there being no difference in blood pressure between the two groups, there was a significant reduction in 24-h urinary protein excretion in the losartan group ($n = 43$), but there was no change in the amlodipine group ($n = 43$). Analysis of stratified subgroups with proteinuria of 2 g or more/day and less than 2 g/day showed that losartan lowered proteinuria by approximately 24% in both subgroups, while amlodipine lowered proteinuria by 10%, but only in the subgroup of less than 2 g/day (NS). SCr and CCr did not change throughout the period of 3 months in either group. No severe or fatal adverse event was experienced in either group during the study period.

Conclusions. Losartan appeared to be efficacious for renoprotection in patients with proteinuric CKD and hypertension, with the mechanism being independent of its antihypertensive action.

Key words Losartan · Amlodipine · Proteinuria · Kidney · Creatinine · Angiotensin · Hypertension

Introduction

Evolution of research of the renin angiotensin system (RAS) has provided a great deal of evidence covering fields from molecular biology to clinical medicine. Based on experimental and clinical evidence of the effects of angiotensin II on cardiovascular physiology, hypertension and related cardiovascular diseases have been the most important targets of research. The crucial roles of RAS in the pathophysiology of such diseases and the therapeutic benefits of pharmacological intervention in the RAS have now been extensively documented.[1,2] On the other hand, although the direct actions of angiotensin II in hemodynamic and nonhemodynamic aspects of renal physiology are well established, and there is evidence of the close relationship between high blood pressure and renal disease, the role of angiotensin II in the pathophysiology of many types of renal disease is still not clearly explained, because the features of these diseases are complex and evidence of how and to what extent the RAS is involved is still limited.

Renal failure, or renal insufficiency, is known to be a life-threatening disease, especially when the disease shows acute or chronic progression. In this disease, proteinuria per se plays a key role in the progression,[3–6] eventually leading to endstage renal disease (ESRD). Diabetic nephropathy is considered to be responsible for many causative diseases of ESRD worldwide; however, nondiabetic chronic renal diseases also lead to ESRD.

Renal insufficiency is, in a large majority of cases, accompanied by high blood pressure. High blood pressure is a factor leading to renal injury, and conversely, renal insufficiency can cause hypertension. Thus, the two critical factors act synergistically to cause deterioration of the kidney disease toward the terminal stage.

Compelling arguments have been made that aggressive control of blood pressure is important to prevent the progression of kidney disease to ESRD.[7,8] Based on this concept, antihypertensive agents have been widely used to treat patients with kidney disease and hypertension. It has been conjectured that antihypertensive agents improve systemic and renal hemodynamics, and prevent glomerular protein leakage through a reduction of high filtration pressure.

However, whether the blood-pressure lowering effect of antihypertensive agents shows parallelism with the renoprotective effect is still controversial. In this view, current evidence of the involvement of angiotensin II in the pathophysiology of renal disease has led to an interest in comparing the effect of intervention in the RAS with the effect of other conventional antihypertensive agents. Although several clinical trials comparing the effects of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (AIIAs) with β-blockers or calcium channel blockers (CCBs) in patients with renal disease and hypertension have been reported,[8–10] only limited information has been available about the potential renoprotective efficacy of AIIAs in Japanese patients with chronic kidney disease (CKD) and hypertension. The present clinical trial therefore aimed to elucidate the effect of the AIIA losartan on renoprotection, comparing it with the effect of the dihydropyridine CCB amlodipine in Japanese patients with CKD manifesting proteinuria and hypertension. The study protocol was designed to pursue the effect of losartan and amlodipine for 12 months, with interim analysis at 3 months and follow-up analysis at 12 months. We herein report the result of the interim analysis at 3 months, because the amelioration of proteinuria was achieved by losartan at this point of time.

Methods

Patients

Patients, men and women, aged ≧20 to <75 years, who had CKD and hypertension were eligible for the study, if they satisfied the following criteria during the pretreatment screening period of 8 weeks:

(a) CKD; serum creatinine (SCr) levels were $1.5 \leqq SCr < 3.0$ mg/dl in men of body weight (BW) 60 kg or more, and $1.3 \leqq SCr < 3.0$ mg/dl in females or males of BW less than 60 kg.
(b) Hypertension; systolic (SBP) and diastolic (DBP) blood pressures in a sitting position measured at least two times at their visits to clinics were SBP, 140 mmHg or more or DBP, 90 mmHg or more.
(c) Proteinuria; urinary protein excretion was 0.5 g or more/day.

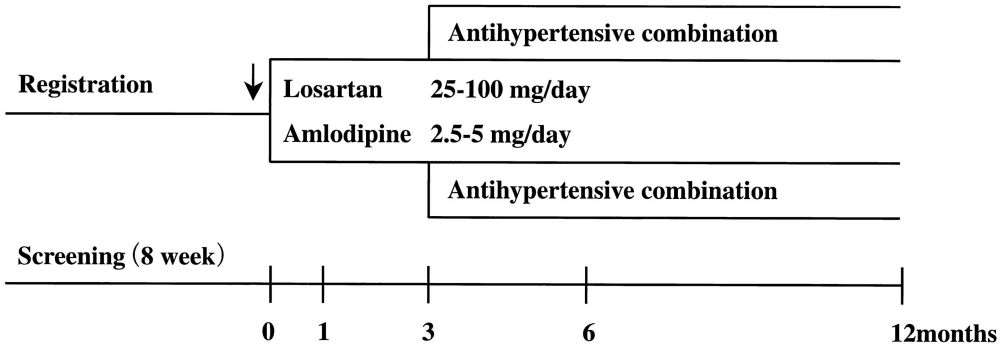

Fig. 1. Study design for treatment of patients with proteinuric chronic kidney disease (CKD) and hypertension. Antihypertensive combination therapy was allowed after the first 3-month period, if necessary (see text)

Study design and clinical endpoints

The overview of the study design is shown in Fig. 1. This study was a randomized parallel-group open-labeled trial with the two drugs. The randomization method was modified by dynamic balancing for SCr, by 24-h urinary protein excretion measured at the time of registration, and by allocating patients with or without diabetic nephropathy so that patients were allocated to the two groups to avoid significant differences. After the screening period, patients in the two groups received either losartan 25 mg as a starting dose, up to 100 mg once daily, or amlodipine 2.5 mg as a starting dose, up to 5 mg once daily. However, if the patients' compliance was considered to be fair to receive higher doses, either 50 mg of losartan or 5 mg of amlodipine was adopted as a starting dose. During the first 3 months, the effects of blood pressure were targeted at SBP less than 130 mmHg and DBP less than 85 mmHg, and patients were not allowed combination therapy with any other antihypertensive agents. However, after 3 months, if the blood pressure did not reach SBP less than 130 mmHg and DBP less than 85 mmHg, antihypertensive combination therapy with α-blockers, β-blockers, α/β-blockers, diuretics (except for potassium-sparing diuretics), and other CCBs was considered to be adopted. Guidance was given to patients to maintain their usual diet, especially for those under dietary restrictions. The study protocol was reviewed and approved by the Institutional Review Boards of 35 affiliated institutions at which patients' enrollment was established for this study. Written informed consents were obtained from the enrolled patients. Exclusion criteria were as follows:

(a) Diastolic blood pressure (DBP, ≧120 mmHg)
(b) Renovascular hypertension and endocrine hypertension
(c) Blood pressure control treatment with antihypertensive agent(s)
(d) Any patients in whom antianxiety drugs could not be discontinued
(e) Pregnancy, possibility of pregnancy, and in a period of lactation
(f) Patients that the chief investigator judged not to be eligible.

Assay parameters

Blood pressure, with the patient in a sitting position, was measured at patients' visit to the clinic.

A 24-h urine collection was performed from 8:00 AM of one day before to 8:00 AM of the day of the clinic visit, to obtain the 24-h urine volume, urinary protein excretion, and the urinary creatinine level, as well as the amount of sodium excretion. The creatinine clearance (CCr) was calculated by the following formula: $CCr = Ucr \times V / SCr \times 1.73/A$, where CCr is creatinine clearance (ml/min); UCr is urinary creatinine (mg/dl), V is urine volume (ml/min); SCr is serum creatinine (mg/dl); and A is body surface area.

Urinary protein, UCr, and SCr levels were determined by a standard method at each center. The magnitude of renal impairment was expressed by the reciprocal of SCr (1/SCr).

Protein and sodium chloride (NaCl) intakes were estimated by measurements of urea nitrogen plus protein concentrations, and NaCl concentrations in the collected urine, respectively, by the following formulas:

Protein intake (g/day)[11]
= [urinary urea nitrogen (g/day) + 0.031(g) × BW (kg)] × 6.25 + urinary protein excretion (g/day)
NaCl intake (g/day)
= urinary sodium excretion (mEq/day)/17.

Statistics

All values were expressed as means ± SD. The baseline characteristics of the enrolled patients were tested for comparability between the losartan group and the amlodipine group, using unpaired *t*-test or Fisher's exact test. The difference in SBP and DBP changes between the losartan group and the amlodipine group was tested by a repeated-measures analysis of covariance with treatment effect, period effect, and center effect. Changes in urinary protein excretion, SCr, and CCr within each group were analyzed by paired *t*-test. Unpaired *t*-test was used to compare the percent changes of urinary protein excretion, SCr, and CCr between the losartan group and the amlodipine group. *P* values of less than 0.05 were considered statistically significant.

Table 1. Baseline characteristics of patients enrolled in the study

	Losartan group ($n = 47$)	Amlodipine group ($n = 46$)	P value
Age (years)	56.0 ± 14.3	57.4 ± 11.7	NS[a]
Male/female	25/22	35/11	$P < 0.05$[b]
BMI (kg/m^2)	24.1 ± 3.9	22.8 ± 3.4	NS[a]
Systolic BP (mmHg)	155.4 ± 10.7	156.1 ± 14.4	NS[a]
Diastolic BP (mmHg)	92.8 ± 8.6	93.6 ± 7.9	NS[a]
Serum creatinine (mg/dl)	2.01 ± 0.51	1.99 ± 0.51	NS[a]
Urinary protein (g/day)	2.64 ± 2.61	2.79 ± 3.72	NS[a]
Serum albumin (g/dl)	3.78 ± 0.47[c]	3.78 ± 0.49[c]	NS[a]
Diagnoses (no. of patients)			
Chronic glomerulonephritis (IgA nephropathy)	27 (8)	30 (12)	
Diabetic nephropathy	7	6	
Hypertensive nephrosclerosis	9	8	
Tubulointerstitial nephritis	2	0	
Polycystic kidney desease	1	0	
Preeclampsia	1	0	
Renal amyloidosis	0	1	
Castleman's disease	0	1	

Mean ± SD
BMI, body mass index; BP, blood pressure; NS, not significant
[a] Unpaired *t*-text
[b] Fisher's exact test
[c] $n = 44$ in each group

Results

A total of 93 patients were enrolled for the present study during the period from December 1999 to September 2001 – 47 in the losartan group and 46 in the amlodipine group. Table 1 shows the baseline characteristics of patients enrolled in the study. The characteristics of the two randomized groups were similar. The dietary compliance assessment by measurements of 24-h urinary urea nitrogen plus protein and sodium showed that there was no significant difference in total protein and NaCl intake between the two groups, nor were there any differences in the values between the baseline and the 3-month values (protein intake [g/day], losartan, 53.71 ± 17.35 [baseline], 52.76 ± 15.69 [3 months]; amlodipine, 53.30 ± 16.48 [baseline], 55.64 ± 20.23 [3 months]; NaCl (g/day), losartan, 7.85 ± 3.37 [baseline], 7.69 ± 3.62 [3 months]; amlodipine, 9.62 ± 4.91 [baseline], 9.16 ± 5.08 [3 months]). At the time point of the 3-month analysis, 43 patients in the losartan group and 43 in the amlodipine group were available for analysis of the measured parameters and their corresponding statistics. Of the total of 93 patients recruited for the study, 86 patients (43 patients each for the losartan group and the amlodipine group) were available for measurement of the urinary protein endpoint.

The blood-pressure-lowering effect, for both SBP and DBP, was similar with losartan and amlodipine. Figure 2 shows changes in SBP and DBP, during treatment for 3 months with losartan and amlodipine. In the losartan group, SBP was reduced from 155.4 ± 10.7 mmHg at baseline to 141.0 ± 16.2 mmHg at 3 months (−8.9 ± 8.7%), and DBP was reduced from 92.8 ± 8.6 mmHg at baseline to 84.3 ± 8.6 mmHg at 3 months (−9.1 ± 9.4 %). In the amlodipine group, the reduction in SBP was from 156.1 ± 14.4 mmHg at baseline to 137.6 ± 13.9 mmHg at 3 months (−11.1 ± 8.8%), and DBP was reduced from 93.6 ± 7.9 mmHg at baseline to 83.1 ± 8.1 mmHg at 3 months (−11.3 ± 9.2 %).

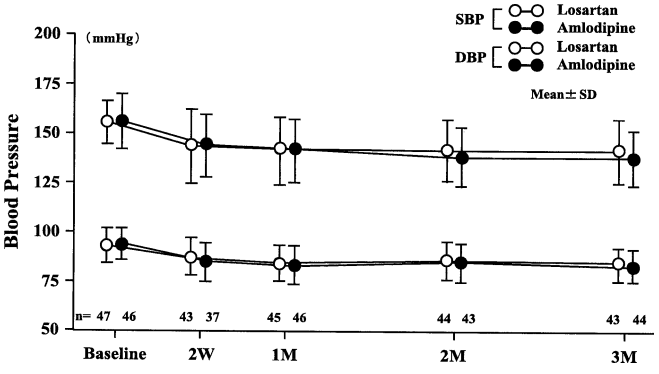

Fig. 2. Systolic blood pressure (*SBP*) and diastolic blood pressure (*DBP*) changes during 3 months in groups treated with losartan and amlodipine. *W*, weeks; *M*, months

However, proteinuria was reduced more with losartan than with amlodipine. As shown in Fig. 3a, the urinary protein excretion in a large number of individuals in the losartan group showed a rightward decline, resulting in a significant decrease in the average protein excretion from the baseline to the 3 months, while in the amlodipine group individuals showed dispersion. As a result, as shown in Fig. 3b, the mean percent change of urinary protein excretion from the baseline was evident in the losartan group, but there was no statistically significant change in the amlodipine group.

In order to examine whether the severity of proteinuria affected the result of treatment with losartan and

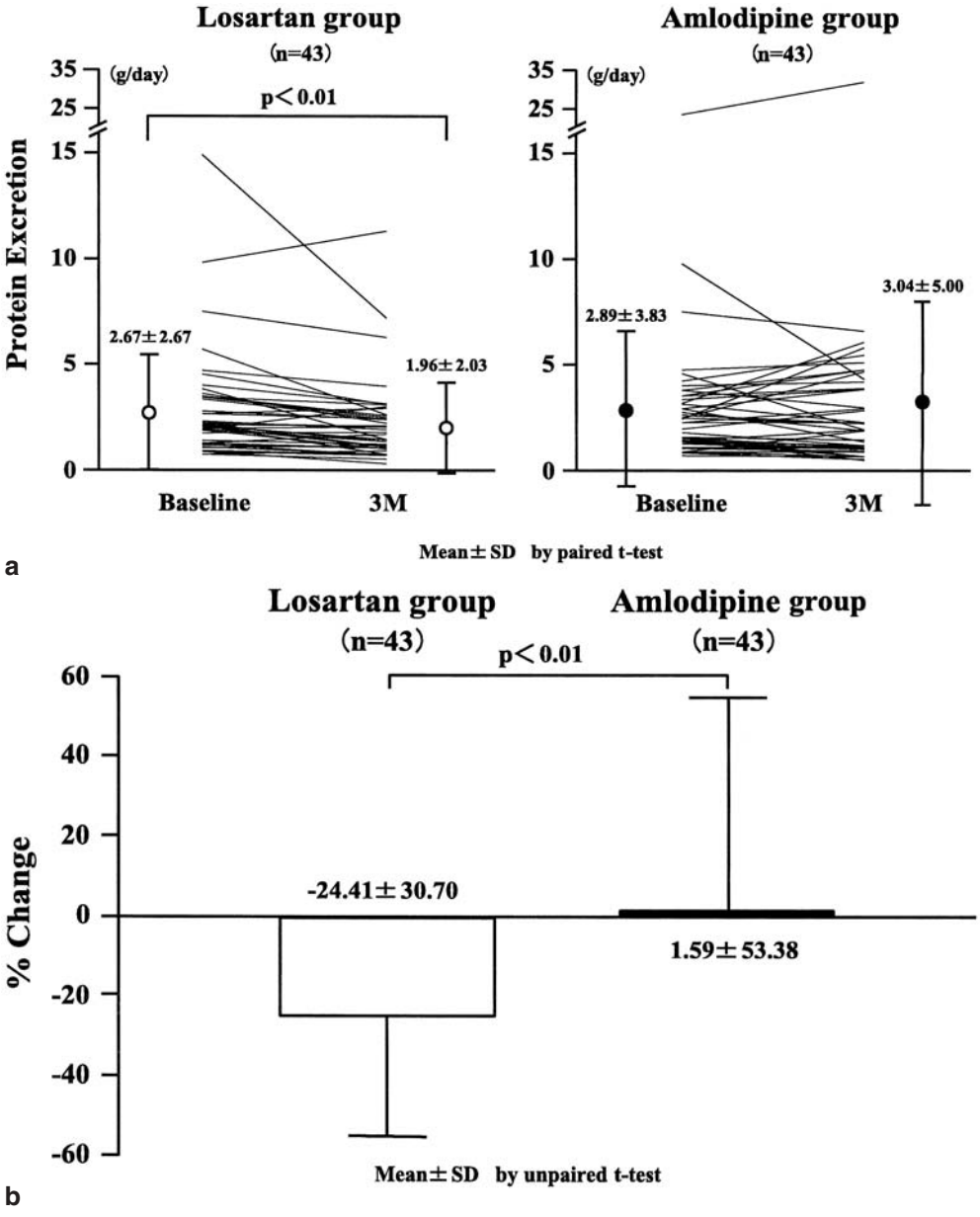

Fig. 3a,b. Changes in 24-h urinary protein excretion from baseline to 3 months after initiation of treatment with losartan and amlodipine. **a** Values for protein excretion in individuals in the respective groups. **b** Percent changes compared with the respective baseline values

amlodipine, we stratified patients into two subgroups, those with proteinuria less than 1 g/day and those with 1 g or more /day at baseline. In these subgroups, the change in urinary protein excretion from baseline to 3 months was not statistically significant between the losartan group and the amlodipine group. We next stratified patients with levels of less than 2 g/day and 2 g or more/day at baseline. As shown in Fig. 4, the reduction in urinary protein excretion at 3 months was evident in the losartan subgroups of both less than 2 g/day and 2 g or more/day, while at 3 months, amlodipine did not significantly reduce urinary protein excretion in either subgroup of less than 2 g/day or 2 g or more/day. The percent change in urinary protein excretion showed a significant difference between the losartan group and the amlodipine group of 2 g or more/day, but there was no significant difference between the subgroups of less than 2 g/day.

By diagnosis, 26 patients in the losartan group and 28 in the amlodipine group had chronic glomerulonephritis, and only 6 in each group had diabetic nephropathy. Analysis of the proteinuria subgroups of the 6 patients with diabetic nephropathy showed that there was a slight decrease in urinary protein excretion at the 3 months in both the losartan and amlodipine groups, but there was no significant difference between the two groups (data not shown). Analysis of the proteinuria subgroups in the patients with chronic glomerulonephritis showed that proteinuria was significantly inhibited in the losartan group during the 3 months, while there was no change in the urinary protein excretion in the amlodipine group, resulting in a significant difference between the two groups in terms of the parameter of percent change (Fig. 5).

Figure 6 illustrates changes in SCr and 1/SCr as a function of time elapsed. There was no significant difference in

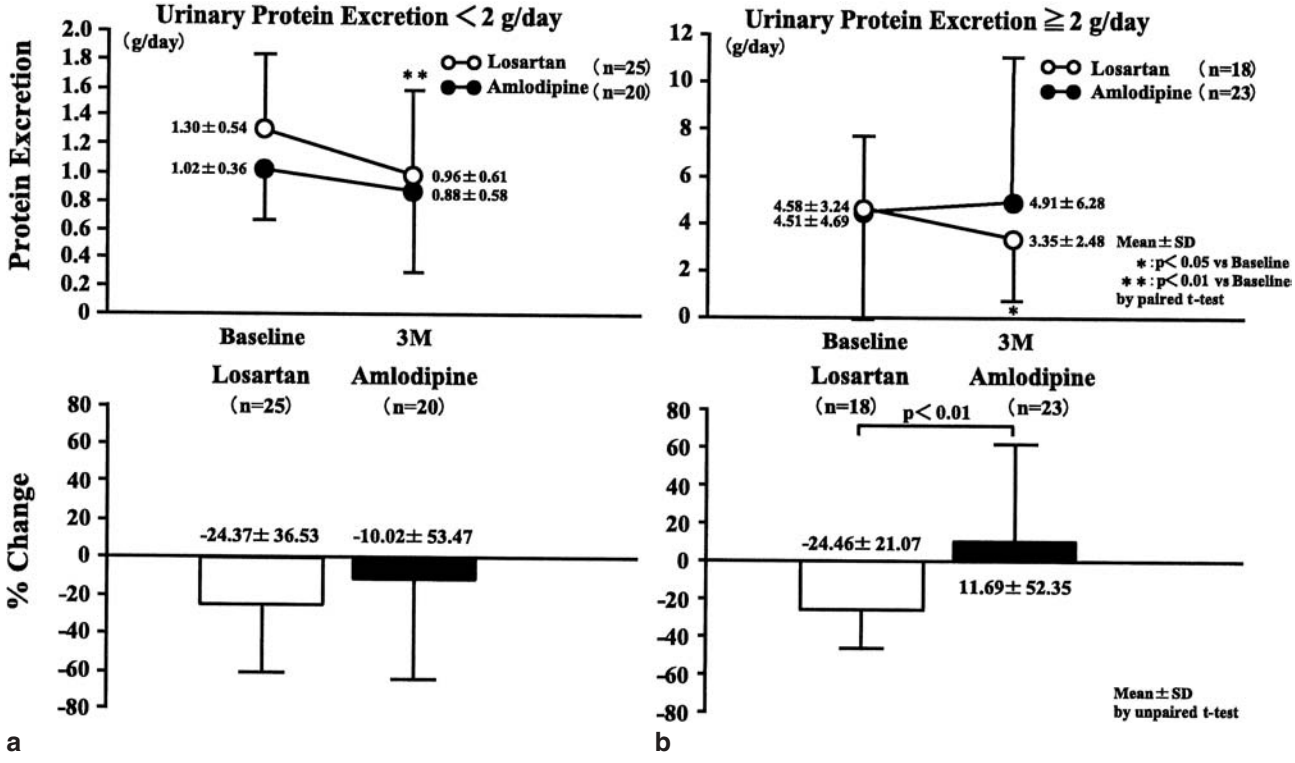

Fig. 4a,b. Changes in 24-h urinary protein excretion from baseline to 3 months after initiation of treatment in the losartan and amlodipine subgroups, showing baseline urinary protein excretion of less than 2 g/day (**a**) and 2 g or more/day (**b**). *Upper panels* Mean values of urinary protein excretion. $*P < 0.05$ vs baseline; $**P < 0.01$ vs baseline. *Lower panels*, Percent changes compared with respective baselines values

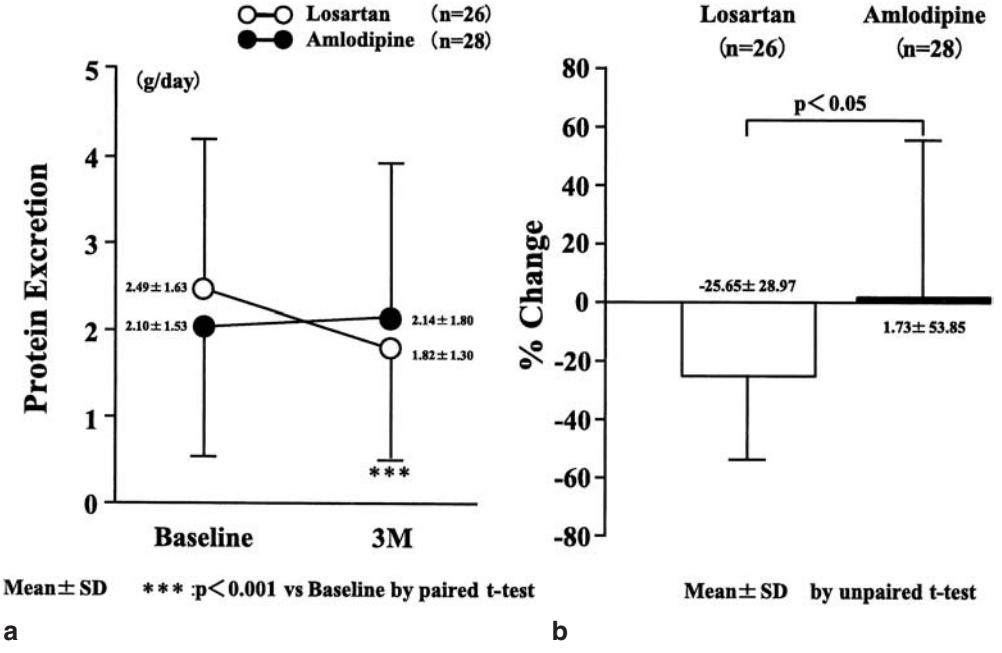

Fig. 5a,b. Changes in 24-h urinary protein excretion in patients with chronic glomerulonephritis from baseline to 3 months after initiation of treatment with losartan and amlodipine. Note that there was no statistically significant difference in baseline protein excretion between the two groups. **a** Mean values of urinary protein excretion. $***P < 0.001$ vs baseline. **b** Percent change in protein excretion compared with the baseline values of the respective groups

the values of SCr and 1/SCr between the two groups, although SCr slightly increased from the baseline to the 3 months in both groups. Also, CCr showed no significant difference between the two groups, either for the values or for percent change (Fig. 7).

Adverse experiences that were considered by the investigators to be possibly related to the study were reported for increases in aspartate aminotransferase (AST; GOT) ($n = 2$), alanine aminotransferase (ALT; GPT) ($n = 1$), and γ-guanosine triphosphate (GTP) ($n = 4$). These experiences

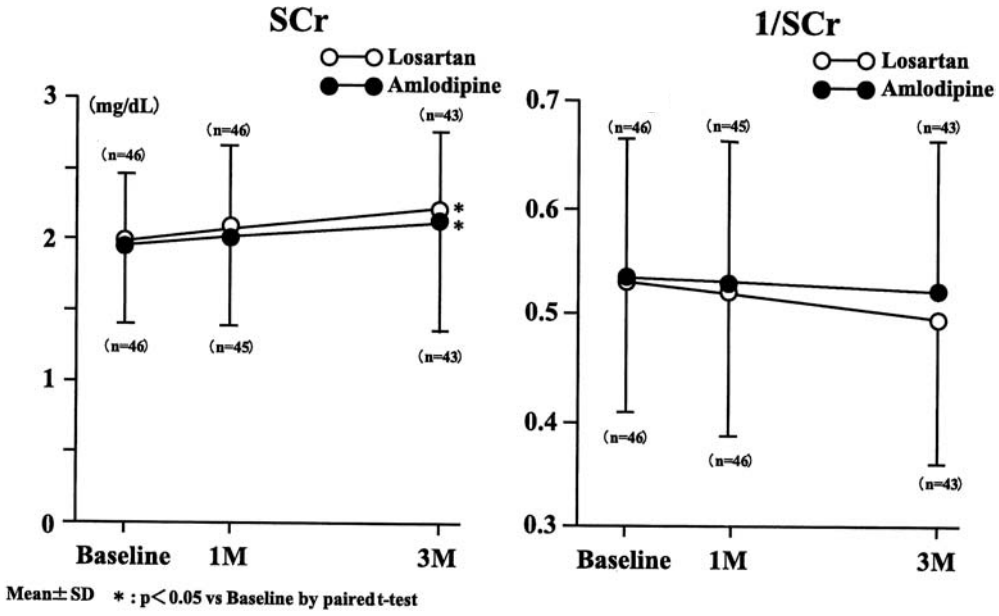

Fig. 6a,b. Changes in serum creatinine levels during 3 months in the losartan and amlodipine groups. *$P < 0.05$ vs baseline. **a** Serum creatinine levels expressed as mg/dl (*SCr*). **b** Values expressed as reciprocal of serum creatinine (*1/SCr*)

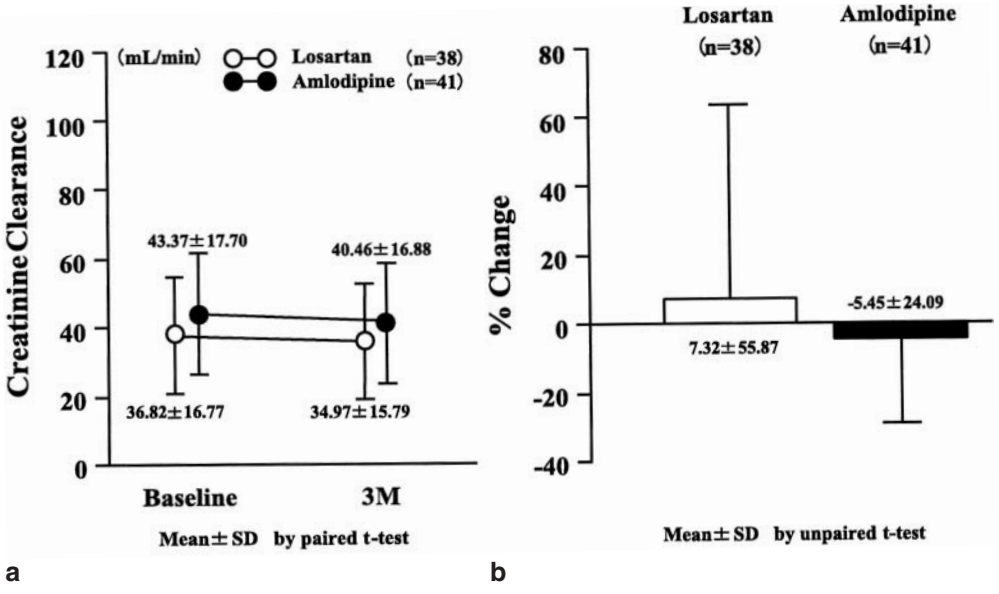

Fig. 7a,b. Changes in creatinine clearance from baseline to the 3 months after initiation of treatment with losartan and amlodipine. **a** Creatinine clearance, in ml/min (CCr). **b** Percent changes in CCr compared with the baseline values of the respective groups

were mild and the incidence was almost the same in the losartan group and the amlodipine group. Hyperkalemia was reported in three patients in the losartan group (5.1, 6.1, and 6.9 mEq/l at 3 months) and in two patients in the amlodipine group (5.9 and 5.2 mEq/l at 3 months). Dizziness ($n = 2$) and transient ischemic attack ($n = 1$) in the losartan group, and an increase in serum uric acid ($n = 2$) in the amlodipine group were reported. No severe or fatal adverse events were observed in either of the groups during the period of 3 months.

Discussion

The present report, although it is the result of the 3-month interim analysis of a total 12-month clinical trial, provides the first evidence that the AIIA losartan is more effective than the CCB amlodipine to ameliorate proteinuria in Japanese patients with proteinuric CKD and hypertension. The difference in the urinary protein-sparing effect between the two drugs was more prominent in patients whose baseline proteinuria was 2 g or more/day. It is noteworthy that the two drugs exerted the same magnitude of systolic and diastolic blood-pressure-lowering effects. Of the 47 patients in the losartan group, 22 were females, while in the amlodipine

group, 11 of the 46 patients were females. It was considered that, in females, a sex hormone such as estrogen per se might act for renal protection through its anti-atherosclerotic effect and other cardiovascular effects; however, a large majority of female patients in the losartan group were over 50 years old (54–59 years, 4; in their 60s, 9; in her 70s, 1), suggesting the presence of menopause. Although there was a possibility that estrogen level in these patients was not negligible, estrogen was not considered to play a protective role against glomerular sclerosis and mesangial proliferation, which are major structural changes associated with CKD-related proteinuria. Thus, it was unlikely that the larger number of female patients in the losartan group gave a bias to the result. Notwithstanding this, we anticipate that, in the final analysis at 12 months, we will pursue the results of female patients separately from those of male patients.

There is controversy regarding the comparative evaluation of various antihypertensive agents such as AIIAs, ACEIs, CCBs, and β-blockers with respect to their potential renoprotective efficacy. Among these agents, the effects of ACEIs as renal protective agents have been widely documented.[12] The renoprotective effect of ACEIs is not exerted solely in diabetic nephropathy, as nondiabetic chronic renal failure was demonstrated to be capable of being treated with ACEIs.[13–16] Many antihypertensive agents have been considered to be effective in patients with renal impairment, most of which were for patients with diabetic nephropathy, given with the expectation of reducing systemic or intraglomerular high blood pressure. In 1998, a result for the clinical trial of the United Kingdom Prospective Diabetes Study Group (UKPDS)[8] was published, which concluded that, in 1148 hypertensive patients with type 2 diabetes, the blood-pressure-lowering effect with captopril and atenolol was similar, and the two drugs also exerted similar effects in reducing the risk of macrovascular and microvascular complications related to this type of diabetes. However, there is a question as to whether all antihypertensive agents exert similar clinicals effect only by reducing systemic or intraglomerular blood pressure.

The RAS is now well understood to be involved in the pathogenesis of renal impairment independently of its vasoconstrictive actions, inducing disturbance of glomerular and tubular functions. The direct actions of angiotensin II in the kidney include an increase in tubular sodium reabsorption and an influence on glomerular filtration rate (GFR), but morphopathological changes such as accumulation of extracellular matrix and mesangial cell proliferation and hypertrophy[17,18] are of more importance for the pathogenesis of renal impairment. Therefore, the question has arisen as to whether pharmacological intervention in the RAS confers an additional benefit beyond the lowering of blood pressure. Based on this view, clinical studies to test the therapeutic effects of drugs that interfere with the actions of angiotensin II, in terms of the direct endpoints of renal function, such as serum creatinine (SCr), creatinine clearance (CCr), and proteinuria, and the ultimate goal, ESRD, have been conducted in patients with diabetic nephropathy. In 2001, the results of two studies to evaluate the clinical effects of AIIA in patients with type 2 diabetes were published, one of which evaluated losartan,[19] and the other, irbesartan.[20] The study with losartan clearly demonstrated that the drug treatment reduced the incidence of the doubling of the SCr level and decreased the amount of urinary protein excretion, and reduced the incidence of ESRD. The study with irbesartan also showed a similar effect for renoprotection by reducing the incidence of severe proteinuria. These two studies clearly demonstrated the advantage of angiotensin II receptor blockade in patients with type 2 diabetes, but no clinical evidence has yet been provided for the effect of angiotensin II receptor blockade in patients with nondiabetic renal failure and related kidney diseases in Japanese. In addition, comparative clinical evidence of the effects of AIIAs and other widely used antihypertensive agents is necessary for the selection of appropriate drugs to treat patients with such kidney diseases.

The African-American Study of Kidney Disease and Hypertension (AASK), a randomized double-blind controlled trial,[9] aimed to compare the effects of the ACEI ramipril with the CCB amlodipine and the β-blocker metoprolol on hypertensive renal disease progression in African-Americans. This study was stopped prematurely because interim analysis showed a slower decline in glomerular filtration rate and a reduced rate of clinical endpoints with ramipril than with amlodipine. However, the results of this study are, in its concept, in accordance with the results of our present study, because intervention in the RAS is better than calcium channel blockade with amlodipine, although our study employed direct angiotensin II receptor blockade with losartan, while the AASK employed ACE inhibition with ramipril.

In our present study, urinary protein excretion was significantly inhibited by losartan in patients with chronic glomerulonephritis, which is very common in Japan (losartan, $n = 26$; amlodipine, $n = 28$). Chronic glomerulonephritis involves many factors in its etiology, and the complicated proteinuria is not solely a result of hyperfiltration by the glomeruli. Rather, remodeling of the glomerulus, including impairment of permeability of the glomerular basement membrane, must be considered. Thus, our present result is of particular interest in considering the direct actions of angiotensin II on the structure and function of the glomerulus in the pathophysiology of the progression of proteinuria in this disease. There was no significant difference in urinary protein excretion between losartan- and amlodipine-treated patients in the subgroup with diabetic nephropathy; however, because only six patients were analyzed in this interim report, we cannot conclude that the effect of losartan and amlodipine is similar for the prevention of proteinuria in diabetic nephropathy.

Throughout the 3 months, there was no change in CCr in either the losartan or the amlodipine group. Andersen et al.[21] conducted a randomized double-blind crossover clinical trial to evaluate the effect of losartan and the ACEI enalapril in patients with type 1 diabetic nephropathy, for 2 months, and reported that intervention in the RAS reduced urinary protein excretion without changing the GFR. Together with our present study, these results suggest

that short-term treatment with losartan is probably effective to ameliorate proteinuria without influencing GFR, although the mechanism of action, including how the drug acts on renal functions or affects the microstructure of the glomerulus during a 2- to 3-month period remains to be elucidated. Our trial will be continued to obtain the 12-month follow-up analysis, and we anticipate that CCr will become different between the two drug-treated groups, reflecting the degree of reduction in urinary protein excretion. Likewise, it may be possible that longterm treatment of the patients with losartan has beneficial effects on renal function beyond the effect to reduce proteinuria.

The mechanism and mode of action of losartan and amlodipine to explain their exertion of different effects on renoprotection are not thoroughly explained, and are controversial. It seems to be true that the actions of angiotensin II to reduce renal function are mediated by angiotensin $(AT)_1$ receptors. Calcium channel blockers act to dilate the microvasculature, improving regional circulation by regulating voltage-dependent calcium channels. The blockade of angiotensin II receptors results in a reduction in renal perfusion pressure, in addition to dilation of the efferent arterioles to a greater extent than afferent arterioles because of their different manner of constriction in response to angiotensin II;[22] thereby, AIIAs reduce the glomerular filtration pressure to some extent. On the other hand, angiotensin II does not act solely to constrict macrovascular and microvascular trees, but has a variety of cellular actions. A number of reports describe the roles of angotensin II through angiotensin $(AT)_1$ receptors to produce extracellular matrix, as well as to stimulate the proliferation and/or hypertrophy of many types of cells, via the direct stimulation of mitogen-activated protein kinase (MAPK), transforming growth factor (TGF-β), nuclear factor (NF-κB), the induction of protooncogenes, and so on.[17,18,23] Thus, although there is still no confirmatory theory, the wider biological functions of angiotensin II may explain the diversity of the renoprotective activity of the two drugs (losartan and anlodipine) without a dependence on their blood-pressure-lowering efficacy. The precise mechanism of action of these drugs should be further investigated. While we were performing the study, Nakao et al.[24] studied the effects of combination therapy and monotherapy with losartan and the ACEI trandolapril in patients with nondiabetic renal disease. In their recently published result, they demonstrated that losartan as well as trandolapril effectively lowered urinary protein excretion, although the combination of these two drugs exerted a more favorable effect on proteinura than either drug alone. Our present result is consistent with their results in terms of the effect of losartan in ameliorating proteinuria in patients with nondiabetic CKD.

In conclusion, by the 3-month interim analysis of the total 12-month treatment of Japanese patients with proteinuric CKD and hypertension, losartan reduced proteinuria more effectively than amlodipine, although the blood-pressure-lowering effect was not different between the two drug-treated groups. The superiority of losartan was more evident in patients whose baseline urinary protein excretion was 2 g or more /day. Thus, losartan is effective not only for patients with hypertension but also for patients with CKD manifesting proteinuria and hypertension.

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