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Telmisartan in patients with mild/moderate hypertension and chronic kidney disease

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Key words
chronic kidney disease – hemodialysis – telmisartan – angiotensin II receptor blocker – hypertension

Abstract. Aims: This study assessed the clinical efficacy and safety of telmisartan, an angiotensin II receptor blocker with a long terminal elimination half-life and almost exclusively excreted in bile, in patients with varying severity of chronic kidney disease (CKD). Patients and methods: Adults with diastolic blood pressure (DBP) 90 – 109 mmHg and stable CKD were enrolled: mild/moderate (creatinine clearance (CrCl) 30 – 74 ml/min/1.73 m^2), severe (CrCl < 30 ml/min/1.73 m^2) or requiring maintenance hemodialysis. A two- to four-week single-blind, placebo run-in period preceded once-daily telmisartan 40 mg administration for four weeks. Telmisartan 80 mg was given after four- or eight-week treatment if DBP 85 mmHg. After 12-week treatment, trough DBP/systolic blood pressure (SBP), DBP and SBP control rates, renal function and tolerability were recorded. Results: Mean changes in DBP/SBP were –10.5/–10.7 mmHg for mild/moderate CKD (n = 27), –11.2/–14.9 mmHg for severe CKD (n = 27), and –15.0/–21.1 mmHg for hemodialysis patients (n = 28). DBP control rates (< 90 mmHg)/SBP responses (< 140 mmHg or 10 mmHg reduction) occurred in 59.3%/66.7%, 63.0%/70.4% and 71.4%/92.9% of mild/moderate CKD, severe CKD and hemodialysis patients, respectively. Incidences of drug-related adverse events were low, and all were known adverse events of telmisartan and common to other angiotensin II receptor blockers. At the end of treatment, a decrease in 24-h urine creatinine occurred in 5/53 (9.4%) patients. Two patients discontinued treatment prematurely due to the worsening of CKD and one due to aggravated proteinuria. Conclusion: Once-daily telmisartan provided effective and well-tolerated treatment of mild/moderate hypertension in CKD patients, with no worsening of renal function.

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■■■?Introduction

Chronic kidney disease (CKD) is a worldwide problem, being under-diagnosed and under-treated; as a consequence, decreased kidney function can lead to life-threatening disease. Because hypertensive patients are at increased risk of progressive CKD, rigorous control of blood pressure is essential [Cushman 2003]. Blockade of the renin-angiotensin-aldosterone system reduces blood pressure and inhibits other pathophysiologic actions, such as endothelial dysfunction and vascular remodeling [Schiffrin 2002].

The antihypertensive agent telmisartan is a highly lipophilic angiotensin II receptor blocker (ARB) [Wienen et al. 2000]. Telmisartan binds selectively and insurmountably to the angiotensin type 1 (AT_1) receptor, has a high volume of distribution, and a long terminal elimination half-life [Sharpe et al. 2001]. Excretion, in contrast to other ARBs [Sica and Gehr 2002], is almost exclusively via bile [Stangier et al. 2000a]. In animal models of hypertension, telmisartan displays renoprotective effects [Böhm et al. 1995, Wienen et al. 1999]. Histologic evidence suggests that renoprotection afforded by telmisartan is superior to that of lisinopril [Wienen et al. 1999]. Large-scale, double-blind, randomized, multicenter clinical trials performed in mild/moderate hypertensive patients have established that once-daily telmisartan 40 or 80 mg is effective in controlling blood pressure [Sharpe et al. 2001]. Also, placebo-controlled studies show that telmisartan has a tolerability profile similar to that of placebo [Sharpe et al. 2001].

A previous clinical study conducted in 83 hypertensive patients with stable moderate CKD compared telmisartan 40 – 80 mg with

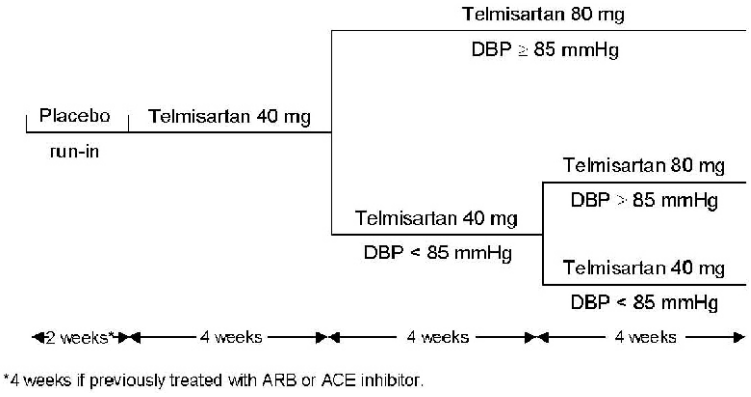

Figure 1. Design of the Efficacy and Safety in Patients with Renal Impairment treated with Telmisartan (ESPRIT) study.

enalapril 10 – 20 mg (in both treatment arms, there was the option to add furosemide to achieve target blood pressure). Telmisartan was as effective in reducing blood pressure and as safe and well-tolerated as enalapril [Hannedouche et al. 2001].

A pharmacokinetic study conducted in six hemodialysis-dependent, normotensive subjects receiving a single oral dose of telmisartan 120 mg showed that the maximum plasma concentration and the plasma concentration-time profile over 24 h after dosing were approximately four-fold lower than values obtained in healthy controls [Stangier et al. 2000b]. It was assumed that the decrease in total plasma levels was at least compensated by a doubling of the free, non-protein-bound concentration of telmisartan. Dosage adjustment is not required for patients with renal dysfunction. Very recent studies provide some evidence of the efficacy of telmisartan in patients with advanced stages of CKD or undergoing hemodialysis. In a study of ten patients with non-diabetic or diabetic nephropathy (proteinuria 1 g/24 h), addition of telmisartan to existing antihypertensive combination therapy significantly reduced daytime and nighttime SBP and DBP [Weinbergová et al. 2004]. Telmisartan also proved more effective than losartan in the treatment of hypertension in dialysis patients [Cice et al. 2004].

The Efficacy and Safety in Patients with Renal Impairment treated with Telmisartan (ESPRIT) open-label, multicenter study was conducted to investigate the antihypertensive efficacy and safety of once-daily telmisartan 40 – 80 mg given for 12 weeks in patients with mild/moderate hypertension and mild/moderate to end-stage CKD.

Methods

Study design

The design of this prospective, open-label study, which was conducted in nephrology clinics in Germany, France and The Netherlands, is outlined in Figure 1. The study received local Ethics Committee approval. Initially, there was a two-week, single-blind, placebo run-in period. This was extended to four weeks if a patient had been previously treated with an ARB or angiotensin-converting enzyme (ACE) inhibitor. The subsequent active treatment period lasted for 12 weeks. All patients initially received telmisartan 40 mg. If after four or eight weeks of active treatment diastolic blood pressure (DBP) was 85 mmHg, the telmisartan dose was increased to 80 mg. Down-titration of the dose to 40 mg was permitted if hypotension was suspected, but subsequent up-titration was not allowed. Throughout the trial, use of concomitant -blockers, -blockers, calcium channel blockers, clonidine, minoxidil and diuretics remained unchanged, other medication that affected blood pressure was excluded.

Patients were told to take the study drug with water in the morning between 7:00 a.m. and 10:00 a.m. If the dose was missed, patients were instructed to take the next dose as scheduled. On the days of clinic visits which were scheduled for between 8:00 a.m. and 10:00 a.m., medication was not taken until after blood pressure measurement to ensure trough values.

Patients

Adult (18 years old) inpatients or outpatients attending a nephrology clinic with mild/moderate hypertension (seated mean DBP 90 – 109 mmHg at the end of the placebo run-in period) and mild/moderate CKD (CrCl 30 – 74 ml/min/1.73 m^2), severe CKD (CrCl < 30 ml/min/1.73 m^2), or requiring maintenance hemodialysis were eligible for inclu-

Table 1. Mean ± SD patient demographics and baseline characteristics.

	Mild/moderate CKD (n = 27)	Severe CKD (n = 27)	Hemodialysis (n = 28)	Total (n = 82)
Age (years)	54.4 ± 11.6	57.6 ± 13.5	48.4 ± 16.1	54.3 ± 14.3
BMI (kg/m^2)	27.9 ± 4.6	27.7 ± 4.3	25.8 ± 4.6	27.1 ± 4.6
Duration of hypertension (years)	11.4 ± 8.3	14.9 ± 12.6	11.1 ± 9.4	12.5 ± 10.3
Duration of CKD (years)	7.1 ± 7.2	6.6 ± 4.4	8.6 ± 7.5	7.5 ± 6.5
Creatinine clearance (ml/min/1.73 m^2)	49.8 ± 22.6	20.0 ± 6.3	–	34.9 ± 22.2
SBP (mmHg)	154.3 ± 13.5	155.6 ± 12.7	158.0 ± 11.8	156.0 ± 12.6
DBP (mmHg)	97.5 ± 5.0	96.8 ± 5.0	95.2 ± 5.9	96.5 ± 5.4
Prior antihypertensive therapy				
ACE-I	44.4%	37.0%	35.7%	39.0%
ARB	14.8%	18.5%	32.1%	22.0%
-blocker[a]	11.1%	7.4%	7.1%	8.5%
CCB[a]	11.1%	7.4%	7.1%	8.5%
Diuretic[a]	3.7%	7.4%	7.1%	6.1%
ACE-I + diuretic[b]	11.1%	7.4%	3.6%	7.3%
ARB + diuretic[b]	7.4%	11.1%	0%	6.1%
ACE-I + CCB[b]	11.1%	0%	0%	3.7%
CCB + -blocker[a]	0%	3.7%	0%	1.2%
Other[a]	7.4%	0%	7.1%	4.9%

SBP = systolic blood pressure, DBP = diastolic blood pressure, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, CKD = chronic renal disease, [a] = treatment maintained during study, [b] = treatment with ARB/ACE-I only discontinued during study.

sion. Patients were required to be in a stable condition, with < 30% increase of serum creatinine in the six months before the trial, serum creatinine of 200 – 600 mol/l or maintenance of hemodialysis, and stable proteinuria of 500 mg/24 h for two months before the trial (non-hemodialysis patients) or no change in the hemodialysis regimen for two months before the trial. Also, patients had to be able to discontinue any previous treatment with an ACE inhibitor or an ARB without jeopardizing their health. Pregnant, breast-feeding or pre-menopausal women not using adequate contraception were excluded. Other exclusion criteria included: mean seated DBP 110 mmHg or mean seated SBP 180 mmHg during the placebo run-in phase, hepatic dysfunction or biliary obstructive disorders, renal artery stenosis, single kidney or kidney transplant, clinically significant electrolyte imbalance, primary aldosteronism, heart failure, unstable angina in previous three months, stroke in the previous six months, or myocardial infarction or cardiac surgery in the previous three months. All patients provided written informed consent at the time of screening.

Patient evaluation

A physical examination was performed at screening (visit 1) and on trial completion, or earlier if the patient withdrew prematurely. Adverse events, concomitant treatment, and vital signs were recorded at each visit. Blood pressure was measured using a cuff sphygmomanometer. Mean blood pressure values were an average of three readings taken at two-minute intervals. Laboratory (blood chemistry, hematology) and renal function (24-h urinary protein, 24-h urinary creatinine) tests were performed at screening, immediately before the start and after 1-, 4- and 12-week active treatment. Blood samples were obtained after overnight fasting and prior to medication. The 24-h urine samples were obtained in the 24-h period before the collection of plasma samples. Urine sampling was performed only in patients with maintained rest-diuresis. Compliance was determined at the end of the placebo run-in and after 4, 8, and 12 weeks of active treatment by monitoring returned medication.

The primary efficacy endpoint was the change from baseline in seated trough (i.e.

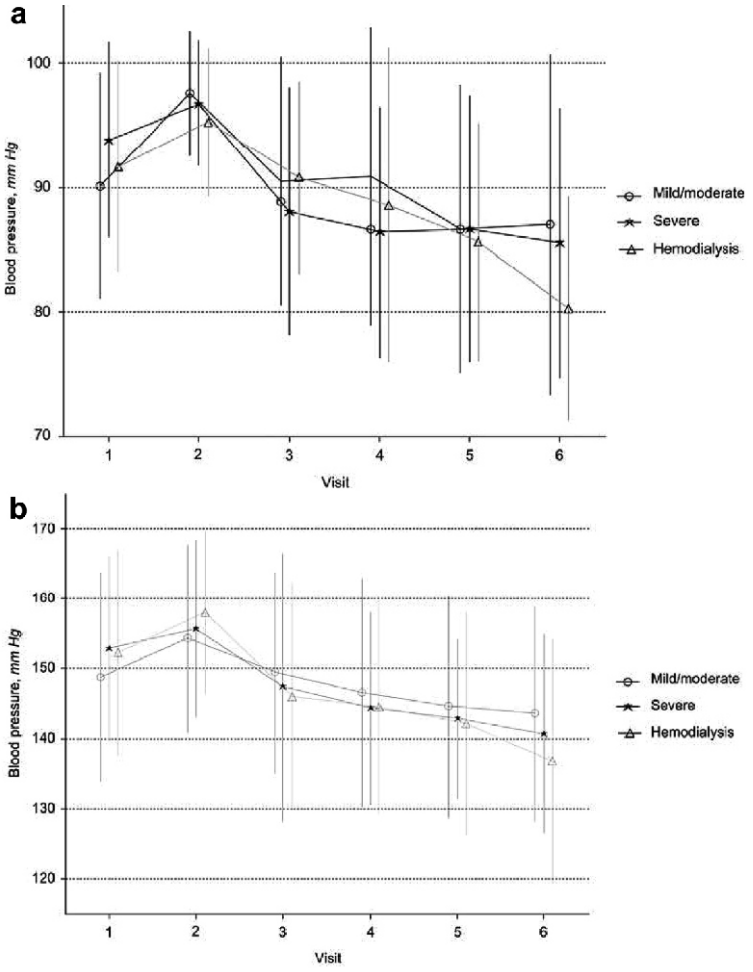

Figure 2. Mean ± SD trough cuff (a) diastolic blood pressure and (b) systolic blood pressure at screening (visit 1), baseline (visit 2) and after 1- (visit 3), 4- (visit 4), 8- (visit 5) and 12- (visit 6) week telmisartan 40 – 80 mg treatment.

23 – 26 h after last dose of medication) cuff DBP after 12-week telmisartan treatment in the full analysis set. If treatment was discontinued prematurely, the last observation was carried forward. Secondary efficacy endpoints were the change in seated trough cuff SBP after 12-week treatment and blood pressure response, defined as: blood pressure normal, SBP < 130 mmHg and DBP < 85 mmHg, DBP control, DBP < 90 mmHg, DBP response, DBP < 90 mmHg and/or DBP reduction of 10 mmHg, SBP response, SBP < 140 mmHg and/or SBP reduction of 10 mmHg, blood pressure high normal, SBP < 140 mmHg and DBP < 90 mmHg.

Safety was evaluated as the incidence, severity and relationship to treatment of adverse events, and as an increase in serum creatinine > 30% and increase in proteinuria compared with from baseline.

Statistical analysis

Baseline demographics were summarized descriptively. To compare the effect of telmisartan within the three strata of CKD (mild/moderate, severe, requiring maintenance hemodialysis), 95% confidence intervals (CI) for the primary endpoint, change from baseline in seated trough DBP after 12-week treatment, were calculated. The same procedure was applied to the change from baseline in seated trough SBP. All patients with baseline and post-treatment measurements were included, in the event of premature withdrawal from the study, the last observation was carried forward. The safety evaluation was performed on all patients who had received at least one dose of active treatment.

Results

A total of 82 patients with long-standing hypertension and associated stable CKD were enrolled and treated with study medication at 15 centers (Table 1). The study was completed by 75 patients. Three patients discontinued prematurely due to an adverse event, two for administrative reasons, one due to non-compliance, and one withdrew consent. There were no relevant statistically significant differences in baseline demographic characteristics between the patient strata (Table 1).

Before the start of the study, 69 (84.1%) patients (24 mild/moderate CKD, 22 severe CKD, 23 maintenance hemodialysis) had received antihypertensive therapy. ACE inhibitors had been used to treat 39.0% of these patients and ARBs to treat 22.0% (Table 1).

Adherence to the dosing regimen was good (97.0% compliance). The telmisartan dose was increased from 40 mg to 80 mg in 41 (50.0%) patients after four- or eight-week treatment. There were no differences in the extent of exposure to telmisartan between the patient strata. During the study, 73 (89.0%) patients maintained their concomitant antihypertensive therapy with diuretics (n = 46), calcium channel blockers (n = 41), -blockers (n = 33), calcium channel blockers in combination with -blockers (n = 2) and others (n = 18).

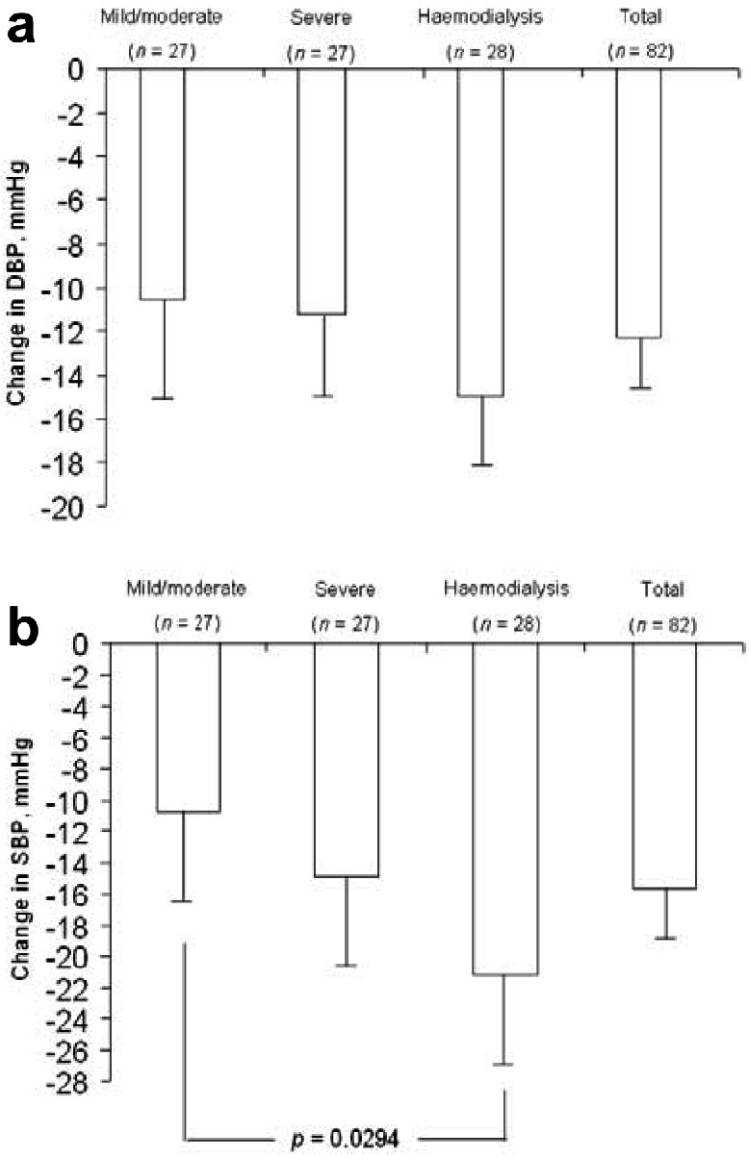

Figure 3. Changes (95% confidence intervals) from baseline in seated trough cuff (a) diastolic blood pressure and (b) systolic blood pressure after 12-week telmisartan 40 – 80 mg treatment.

The overall reduction in trough cuff DBP compared with baseline – the primary efficacy endpoint – was 12.3 ± 9.4 mmHg. In all strata, trough cuff DBP increased during run-in but was reduced with introduction of telmisartan 40 – 80 mg treatment (Figure 2a). A similar pattern of changes in trough cuff SBP was observed (Figure 2b). Telmisartan reduced DBP and SBP compared with baseline after 12-week treatment in all strata (Figure 3). The decreases in DBP for the individual strata were within the 95% CI, thus, there were no statistical differences in blood pressure reductions between the three patient strata. For SBP, pairwise testing was performed for SBP, although the numbers of patients in this trial were too small to guarantee sufficient power. Comparison of mild/moderate CKD patients and hemodialysis patients found that the change in SBP from baseline was significantly greater in the hemodialysis group ($p = 0.0294$). Differences between mild/moderate vs severe and severe vs hemodialysis groups were not significant.

Overall, a DBP response (DBP < 90 mmHg and/or DBP reduction of 10 mmHg) was recorded in 76.8% of patients and a SBP response (SBP < 140 mmHg and/or SBP reduction of 10 mmHg) in 76.8%. Trough blood pressure responses in the three patient strata are summarized in Table 2.

No clinically meaningful variations in pulse rate were noted between screening, baseline and end of active treatment.

Fifty patients among the 82 (61.0%) in the safety population experienced adverse events: one (1.2%) during screening, 14 (17.1%) during run-in, 43 (52.4%) while re-

Table 2. Seated trough cuff blood pressure (BP) responses after 12-week telmisartan 40 – 80 mg treatment.

	Number of patients (%)			
Response	Mild-to moderate (n = 27)	Severe (n = 27)	Hemodialysis (n = 28)	Total (n = 82)
BP normal[a]	3 (11.1)	6 (22.2)	10 (35.7)	19 (23.2)
DBP control[b]	16 (59.3)	17 (63.0)	23 (82.3)	56 (68.3)
DBP response[c]	19 (70.4)	18 (66.7)	26 (92.9)	63 (76.8)
SBP response[d]	18 (66.7)	19 (70.4)	26 (92.9)	63 (76.8)
BP high normal[e]	8 (29.6)	10 (37.0)	14 (50.0)	32 (39.0)

[a] = systolic blood pressure (SBP) < 130 mmHg and diastolic blood pressure (DBP) < 85 mmHg, [b] = DBP < 90 mmHg, [c] = DBP < 90 mmHg and/or a reduction of 10 mmHg, [d] = SBP < 140 mmHg and/or a reduction of 10 mmHg, [e] = SBP < 140 mmHg and DBP < 90 mmHg.

ceiving telmisartan 40 or 80 mg, and three (3.7%, none drug-related) during the post-study period. In 6/82 (7.3%) patients receiving telmisartan 40 mg and in 3/41 (7.3%) patients receiving telmisartan 80 mg, the adverse event was assessed as drug-related by the treating investigator. Adverse events classed as drug-related were known effects of telmisartan listed in the label and consistent with those of other ARBs. In general, the events were mild/moderate in severity. No patient experienced cough. One patient while receiving telmisartan 40 mg experienced serious syncope, hypotension, and hypoglycemia considered related to treatment.

The incidence of possibly clinically relevant laboratory changes was within the range expected, considering the underlying and concomitant diseases. Median change in urinary protein from baseline to last value on treatment was –72.5 mg/24 h. Increased proteinuria occurred in two patients (serious in one) receiving telmisartan 40 mg. Serum creatinine was increased in one patient receiving telmisartan 40 mg and another receiving telmisartan 80 mg. Median changes in urinary creatinine and CrCl from baseline to last value on treatment were –0.12 mmol/24 h and –0.8 ml/min. In 5/53 (9.4%) patients, there was a possible clinically significant decrease in 24-h creatinine excretion at the end of treatment.

Treatment was discontinued prematurely in two patients due to an increase in serum creatinine. Aggravated proteinuria resulted in one patient discontinuing telmisartan 40 mg.

Discussion

The results of the present ESPRIT study demonstrate that once-daily telmisartan 40 – 80 mg is effective in the treatment of mild/moderate hypertension in patients with concurrent CKD. During the study, no patient was withdrawn due to lack of antihypertensive efficacy. The findings are consistent with those of a double-blind, randomized study in patients with moderate CKD, defined as a CrCl of 30 – 80 ml/min [Hannedouche et al. 2001]. In that study, the initial treatment was either telmisartan 40 mg or enalapril 10 mg, with up-titration after four weeks to telmisartan 80 mg or enalapril 20 mg, respectively, if supine trough DBP was 90 mmHg. If the target DBP was not achieved after a further four weeks, addition of furosemide was permitted. Telmisartan proved as effective as enalapril, with fewer patients in the telmisartan group requiring furosemide to achieve the target DBP. The present study confirms telmisartan's efficacy and shows that blood pressure lowering is independent of the CKD severity.

It is notable that the hemodialysis patients experienced greater reduction in blood pressure than those with mild/moderate CKD, although this difference was not statistically significant in the case of the predefined primary efficacy endpoint – change from baseline in DBP. Although the number of patients in the trial was too small to ensure sufficient statistical power, in the case of SBP, the greater change for baseline in the hemodialysis group compared with the mild/moderate CKD group did achieve statistical significance. The numerically greater reduction in blood pressure may be partly attributed to the fact that the patients undergoing hemodialysis had a higher baseline blood pressure. It is a common observation in clinical studies evaluating antihypertensives that greater blood pressure reduction is achieved in more severely hypertensive subjects. Furthermore, hemodialysis patients retain the ability to secrete renin and usually produce inappropriately high levels [Doulton and McGregor 2004 ■■■ not in reference list!]. Treating hypertension using an agent that targets the renin-angiotensin system may, therefore, result in greater reductions in blood pressure. The enhanced efficacy in hemodialysis patients may also be due to the doubling of unbound telmisartan observed in normotensive hemodialysis patients [Stangier et al. 2000b].

The current study used more stringent targets for blood pressure control than the previous study evaluating telmisartan [Hannedouche et al. 2001], although not as rigorous as those recommended in recently published guidelines [Chobanian et al. 2003]. Benefits of lowering blood pressure in patients with CKD to prevent the CKD progression and reduce cardiovascular risk are well-recognized.

To achieve blood pressure control, it is increasingly acknowledged that a combination of agents with different mechanisms of action should be used [Bakris 2003]. This was rec-

ognized in the design of ESPRIT, as patients were allowed to continue treatment with -blockers, -blockers, calcium channel blockers, clonidine, minoxidil and diuretics. No other drugs that affect blood pressure were permitted while being treated with telmisartan. At the end of placebo run-in period, an increase in both DBP and SBP was recorded as the result of withdrawal of ACE inhibitors or ARBs. With the introduction of telmisartan treatment, a reduction in blood pressure was achieved with lower values than were recorded at screening. This suggests that telmisartan provides additional trough blood pressure control. The efficacy of telmisartan is confirmed by the DBP and SBP responses.

Telmisartan was well-tolerated in this study. The incidence of drug-related events was low and all were within the known adverse event profile [Sharpe et al. 2001]. There were no marked differences in the incidences of adverse event in the three patient strata. Most notably there were no reports of cough. A dry, persistent cough occurs relatively frequently with ACE inhibitors [Simon et al. 1992]. For some patients, this negatively impacts on their quality of life to such as extent that they are unprepared to continue treatment [Gavras 2001]. The absence of cough in this study reinforces the findings of an earlier study [Lacourcière and the Telmisartan Cough Study Group 1999].

There were few notable changes in laboratory parameters following telmisartan treatment. These findings are consistent with reports of ARBs' renoprotective properties in diabetic patients [Barnett et al. 2004, Brenner et al. 2001, Lewis et al. 2001, Parving et al. 2001, Viberti and Wheeldon 2002]. The increases in serum creatinine in two patients and increased proteinuria in one patient can be attributed to the severity of the CKD. A possible clinically significant reduction in 24-h urine creatinine was recorded in five patients but there were no instances of poor blood pressure control to explain these changes. ACE inhibitors can induce a reduction in creatinine excretion due to a reduction in the glomerular filtration pressure [Hollenberg et al. 1979].

In conclusion, the ESPRIT study demonstrates that once-daily telmisartan administered at a dose of 40 or 80 mg provides effective blood pressure control and is well-tolerated in patients with varying degrees of CKD ranging from mild/moderate to those requiring maintenance hemodialysis. These data add further evidence that ARBs, particularly telmisartan, can be considered to be first-choice treatment for hypertension in hemodialysis patients.

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