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Effect of telmisartan on kidney function in patients with chronic kidney disease: an observational study

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ABSTRACT

Background: Globally the burden of chronic kidney disease (CKD) is rising, an important cause of death and loss of disability-adjusted life years. Activation of the renin-angiotensin-aldosterone system is involved in its pathogenesis. The aim of the present study was to examine the effects of telmisartan (40 mg/day), an angiotensin receptor blocker (ARB) in Indian patients with CKD in real-life setting.

Method: This was a prospective observational study. Fifty-six patients (>18 years) diagnosed with CKD were enrolled into the study. Serum creatinine, 24-h urinary protein, spot urine protein-to-creatinine ratio, glomerular filtration rate (GFR) and blood pressure (BP) were assessed along with safety.

Results: A total of 55 patients (96.36% hypertensive; 63.61% diabetic) with mean age of 48.23 years completed the study. At the end of 3 months treatment with telmisartan, 24-h urinary protein, spot urine protein-to-creatinine, serum creatinine and BP significantly reduced ($p < .05$) by 806.78 mg, 0.95, 0.44 mg/dl and 8.9/4.7 mmHg in the overall population. GFR increased from the baseline value of 52.13 to 65.01 ml/min. Telmisartan was well tolerated and treatment was discontinued in one patient because of hyperkalemia.

Conclusion: This study demonstrated that telmisartan effectively and safely reduces proteinuria in chronic kidney disease patients.

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KEYWORDS
Chronic kidney disease; proteinuria; telmisartan

Introduction

Chronic kidney disease (CKD) is the 12th and 17th leading cause of death and disability globally, respectively, and the burden is increasing on the global level.[1] There are more than 100 countries with combined population >600 million that have no provisions for chronic maintenance, dialysis or kidney transplantation. Thus it is a major problem and prevalence continues to rise with increasing elderly population and the number of patients with diabetes and hypertension.[2]

Hypertension accounts for 85% to 95% of patients with CKD. Long-term uncontrolled hypertension, leads to high intra glomerular pressure, causing damage to glomerulus and the glomerular filtration, resulting in abnormally increased amounts of protein in the urine.[3] If diabetic and more so over, uncontrolled, glucose build up in the blood further damages the tiny filters in the kidneys, affecting its ability to filter out waste products and fluids. Microalbuminuria is often the first sign of CKD and proteinuria develops as CKD progresses.[4–6] Other factors causing CKD are obesity, glomerulonephritis, systemic lupus erythematous and blockages, for example, due to kidney stones or prostate disease.[7] Reduction in proteinuria correlates with slowing the progression of kidney disease. Moreover, clinical studies including meta-analysis of large-scale studies showed that preservation of the estimated glomerular filtration rate (eGFR) and reduction in proteinuria/albuminuria are important for the suppression of CKD progression in CKD patients.[8,9]

Activation of the renin-angiotensin-aldosterone system (RAAS), especially angiotensin-2 is involved in CKD pathogenesis and its cardiovascular complications.[10] Drugs interfering with the renin-angiotensin system, i.e. angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs) are of choice as they have a blood pressure-independent antiproteinuric effect. During therapy with ACE inhibitors, angiotensin II escape prevents complete RAAS inhibition, due to alternative non-ACE pathways. However, ARBs overcome this limitation by selective blockade of the AT1 receptor and therefore angiotensin II escape observed with an ACEI do not occur with an ARB.[11,12] They are used to maximize RAAS inhibition and more effectively reduce proteinuria and decrease in GFR in diabetic and nondiabetic renal disease.[10] ARBs reduce protein excretion by approximately 35% to 40%, which is greater than other antihypertensive agents.[13] As CKD continues to rise, measures to prevent disease progression is an important goal. Among RAAS inhibitors, ARBs are preferred because of advantage discussed earlier and also because of the fact that

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ACE inhibitors are known to cause dry cough in a higher proportion of the Asian population. Literature search did not reveal specific study with telmisartan carried out in real-life setting in Indian patients. The aim of the present study was to examine the effects of telmisartan in patients with CKD.

Methods

Study design

This was a prospective observational study conducted at Krishna Institute of Medical Sciences Hospital in Nephrology Unit, Hyderabad, India, according to a protocol approved by the Institutional Review Board. The study was carried out in accordance with the Basic Principles defined in the International Conference on Harmonisation 'Guidance for Good Clinical Practice' and the principles enunciated in the Declaration of Helsinki. All the patients provided written informed consent before entering the study.

Patients

Fifty-six patients of either gender diagnosed with CKD and >18 years of age were enrolled into the study. CKD was diagnosed by the presence of proteinuria urinary protein excretion rate ≥0.15 g/day creatinine or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2.

Exclusion criteria included patients on dialysis, women who were nursing or pregnant and those with clinically significant heart disease, stroke, renal artery stenosis, hepatic dysfunction or known hypersensitivity to any ingredient in the study medication. The patients with psychiatric illness that impairs the ability to provide written informed consent, history of drug or alcohol abuse and who were unwilling to give informed consent were also excluded.

Treatment

The patients were treated with telmisartan 40 mg daily for three months. Compliance was assessed by interviewing and questioning the patients during the study period.

Efficacy and safety measurements

The primary efficacy parameter was 24-h urinary protein. The secondary efficacy parameters were serum creatinine, spot urine protein-to-creatinine ratio, GFR and blood pressure (BP). All the patients were monitored throughout the study period for adverse events. The patients were specifically asked about any adverse events on hospital visit.

Statistical analysis

All the results are expressed as mean ± S.D. The demographic and other baseline characteristics of the patients (e.g. age, gender, etc.) are summarized using descriptive statistics. Change from baseline war calculated for creatinine, GFR, 24-h urinary protein, spot urine protein-to-creatinine ratio and BP. Whenever change from baseline was calculated, only those patients for whom baseline and post- treatment assessment (at 3 month) are available were included in the analysis. Student *t*-test was used to compare the baseline and post-treatment values for each variable. The significance of difference was assessed at $p < .05$. Adverse events experienced by the patients during the course of the study were appropriately summarized and tabulated.

Results

Patient characteristics

A total number of 77 patients with CKD were screened and 56 patients were enrolled according to the inclusion and exclusion criteria. One patient was withdrawn from the study and therefore a total of 55 patients completed the study. The mean age of the patients was 48.23 years and 96.36% and 63.63% of the patients were hypertensive and diabetic, respectively. The mean BP before entry into the study was 144.9 ± 12.6/90.6 ± 7.1 mmHg. The causes of CKD in the patient enrolled were hypertension and diabetes. At the time of entry into the study, all the hypertensive patients were being treated with at least one antihypertensive and with oral hypoglycemic agents for those who were diabetic. Detail demographic of the patients is presented in Table 1.

Efficacy endpoint

24-h Urinary protein: At the end of 3 months treatment with telmisartan, 24-h urinary protein significantly reduced ($p < .05$) in the overall patient population. The difference between baseline and end of 3 months treatment was 806.78 mg. Figure 1 shows the changes in urinary protein from the baseline to 3 months.

Spot urine protein-to-creatinine ratio: At baseline spot urine protein-to- creatinine ratio was 1.75 ± 0.9 and reduced to 0.80 ± 0.65 at the end of 3 months treatment. The difference between baseline and end of 3 months was statistical significant (0.95 ± 0.25; $p < .05$).

Serum creatinine: At the end of 3 months treatment, serum creatinine reduced from 1.85 ± 0.67 to 1.41 ± 0.55 mg/dl and the difference was significant ($p < .05$; Figure 2).

GFR: At the end of 3 months treatment, GFR increased from the baseline value of 52.13 ± 17.59 to 65.01 ± 17.90 ml/min. The difference between baseline and at the end of 3 months was statistically significant ($p < .05$).

Table 1. Demographic and baseline characteristics of the patients.

Parameters	Mean ± SD
Age, years	48.23 ± 14
Male	34 (61.18%)
Female	21 (38.10%)
Diabetes mellitus	35 (63.63%)
Hypertension	53 (92.72%)
Diabetes mellitus & hypertension	33 (60.00%)
Serum creatinine, mg/dl	1.851 ± 0.673
GFR, ml/min	52.13 ± 17.59.
24-h Urinary protein, mg/g	1710.55 ± 150.21
Spot urine protein-to-creatinine ratio	1.75 ± 0.9

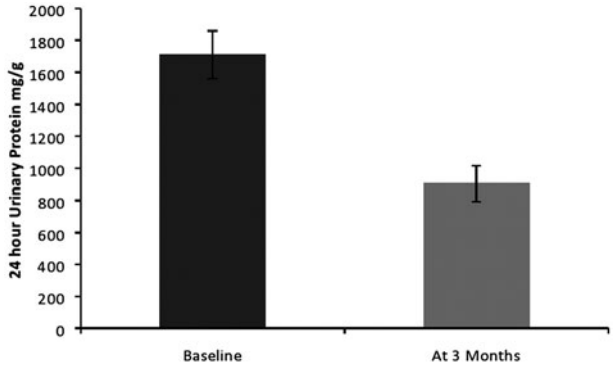

Figure 1. Change in urinary protein from baseline at the end of 3 months treatment.

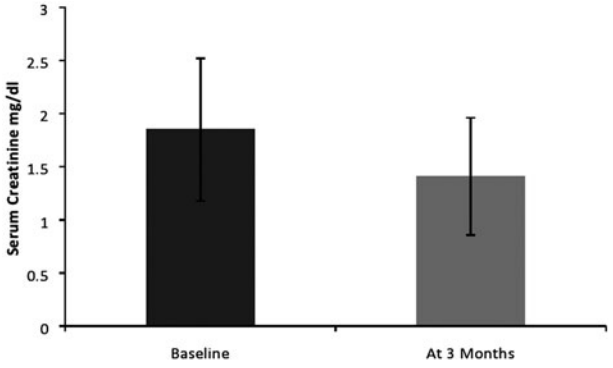

Figure 2. Change in serum creatinine from baseline to end of 3 months treatment.

Blood pressure: Both systolic and diastolic BP decreased significantly ($8.9 \pm 2.6/4.7 \pm 2.1$ mmHg) after 3 months of treatment compared with the baseline value.

Safety endpoint

Telmisartan was well tolerated. Treatment was discontinued in one patient because of hyperkalemia. No other adverse events were reported.

Discussion

Globally the burden of chronic kidney disease is rising, which is an important cause of death and loss of disability-adjusted life-years. RAAS is known to play an important role in CKD [10] and studies have demonstrated a strong association between proteinuria and a more rapid decline in renal function.[14] Any therapeutic intervention, such as inhibition of the RAAS that reduces the level of proteinuria is critically important for regression of the decline in renal function. Studies indicate that ARBs are preferred agents for kidney diseases with proteinuria.[10,11] In this study, 55 patients with CKD were enrolled and treated with telmisartan 40 mg/day. Of the total number of patients enrolled, 96.362% and 63.63% patients were hypertensive and diabetic, respectively. This correlates with the fact that hypertension and diabetes are the leading causes for the kidney damage in developing countries.[15] After 3 months of treatment with telmisartan, significant decrease in urinary protein, serum creatinine, BP and increase in GFR was observed.

Proteinuria magnitude directly influences the rate of renal function deterioration and therefore its satisfactory reduction is considered the primary target for the treatment of patients with CKD[18]. At the end of 3 months of treatment, proteinuria decreased by 19% from baseline suggesting a specific anti-proteinuric effect of telmisartan. In a study comprising of 92 hypertensive proteinuric patients with CKD, a similar decrease (21%) was reported following treatment with telmisartan 40 mg.[16] In an another study, proteinuria was reduced by 29.8% after 52 weeks of treatment with telmisartan 80 mg in hypertensive type-2 diabetes patients with overt nephropathy.[17] The greater levels of reduction in proteinuria observed in this study could be because of the higher dose and longer duration of the study. Further, the ONTARGET study has shown that telmisartan provides superior reductions of proteinuria compared with ramipril and is effective in reducing renal endpoints.[18] ARBs have renoprotection and this effect of telmisartan appears to be more potent than that of losartan, candesartan or olmesartan in early-stage DN patients.[19] On the other hand, in nondiabetic patients treated with various ARBs (olmesartan, valsartan, losartan and candesartan), olmesartan was found to decrease urinary protein greater and more rapidly than the other ARBs. The reason for this difference is unclear and was initially attributed to earlier and rapid decrease in blood pressure with olmesartan than that with the other ARBs. However, there could be other reasons as well since 2 years after starting ARB treatment, the degree of decrease in urinary protein was greater than the degree of decrease in blood pressure.[20] Angiotensin receptor blockers mainly act by inhibiting AT-1 receptor of angiotensin II selectively thereby displacing angiotensin II from AT-1 receptors and produce a lowering effect in blood pressure and proteinuria. With respect to proteinuria, previous studies demonstrated that RAS inhibitors provide superior renoprotection in subjects with high urinary protein excretion.[21]

In addition to proteinuria, abnormal elevations of serum creatinine and decrease in GFR, are also important parameters as they are the indicators for evaluation of CKD. Creatinine is produced continuously during normal muscle breakdown, and decreased renal function interferes with the kidneys ability to eliminate creatinine increasing its concentration as GFR declines. In our study, creatinine was significantly reduced by 18% from baseline ($p < .05$). Similarly, serum creatinine levels decreased in hypertensive CKD patients treated with telmisartan 40 mg once daily for 12 months and the decline was significantly greater than in the amlodipine group ($p < .05$).[20] Furthermore, in literature, conflicting results exists with respect to creatinine, while some authors have reported that creatinine did not change significantly, others have reported that creatinine decreased slightly after treatment with telmisartan.[22–24] The precise cause for this discrepant results are unclear it may be partly related to differences in the patient profiles, telmisartan dose, renal function or duration of treatment. In addition, GFR was also found to increase in the present study. The results of the ACCOMPLISH study indicated that preservation

of GFR is important for the suppression of CKD progression.[9] In addition, it is well known that small changes in BP during the course of a study can significantly affect the rate of CKD progression.[25] Both systolic and diastolic BP reduced by 8.9 and 4.7 mmHg levels, respectively in the present study. Taking into account that telmisartan was added to existing antihypertensive therapy and that the patients had proteinuria these results can be considered significant and satisfactory.

Treatment with ARBs was well tolerated. There were no adverse events reported. However, one patient was discontinued from the study because of hyperkalemia. This study demonstrated that telmisartan effectively and safely reduces proteinuria in chronic kidney disease patients. However, while planning this study, no formal sample size calculation was done to estimate the number of patients required and the total number of patient was considered based on the feasibility. In addition, the study was of 3-month duration and this limited duration of the study might have not allowed to reach the maximum effect with telmisartan. Hence, future studies with long-term duration are recommended.

Transparency

Declaration of funding

This study was not funded.

Declaration of financial/other interests

The authors and CMRO peer reviewer on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Dr Ashish Agrawal wrote the final draft of the manuscript. All authors were involved in the design, conduct, reviewing of the draft manuscript, and agreed on the final version. Dr Ashish the corresponding author, had final responsibility for the decision to submit the manuscript for publication.

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