

Telmisartan lowers albuminuria in type 2 diabetic patients treated with angiotensin enzyme inhibitors

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Received 03.02.2009
Accepted 14.04.2009
Advances in Medical Sciences
Vol. 54(1) · 2009 · pp 37-40
DOI: 10.2478/v10039-009-0015-6
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ABSTRACT

Purpose: Angiotensin-converting-enzyme inhibitors (ACEIs) provide renal protection in patients with type 2 diabetes and microalbuminuria.

Material and Methods: In the presented study we followed 34 stable, type 2 diabetic patients with persistent albuminuria treated with maximal doses of ACEIs as a part of their anti-hypertensive treatment. Telmisartan – an angiotensin receptor blocker (ARB) - in a dose of 40 mg was added to the treatment and the patients were observed for 12 weeks. We measured creatinine clearance, 24-hour urinary albumin excretion, before and after 12 weeks of combined therapy.

Results: The addition of telmisartan resulted in a significant reduction of albuminuria from median 157 to 67 mg/24h. No change in creatinine clearance was observed (93 vs 97 ml/min).

Conclusion: The addition of telmisartan to a maximum dose of ACEI is safe and results in further albuminuria decrease in patients with type 2 diabetes and incipient nephropathy.

Key words: albuminuria, type 2 diabetes, angiotensin converting enzyme inhibitor, angiotensin receptor blockade

INTRODUCTION

Diabetic nephropathy is one of the most devastating microvascular complications of diabetes and the most common cause of end stage renal disease (ESRD) in Europe and the United States [1-3]. This is due to the fact that diabetes, particularly type 2, is increasing in prevalence. Diabetic patients currently live longer, and patients with diabetic end-stage renal disease are accepted for renal replacement programs. Diabetic nephropathy accounts for about 40% new cases of ESRD and the cost of treatment of diabetic nephropathy is immense. About 30% of patients with type 1 and 2 diabetes develop nephropathy. However, because of a much greater prevalence of type 2 diabetes, such patients constitute most of dialysed diabetic patients.

The earliest clinical evidence of nephropathy is the appearance of persistent microalbuminuria in urine e.g. more than 30 mg/day – the condition is referred to as incipient nephropathy. Without specific intervention, 20-40% of these patients progress to overt nephropathy [3,4].

In addition to being the earliest manifestation of

nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality [5].

Recent studies have demonstrated that the onset and the course of diabetic nephropathy can be ameliorated by several interventions, which have the greatest impact if instituted as early as possible [4,5].

Several clinical studies have shown that higher levels of proteinuria are associated with increased progression of renal and cardiovascular disease, and that reductions in proteinuria are associated with a decrease in the rate of renal function deterioration and the incidence of cardiovascular events [4-6].

Reduction in blood pressure has been shown to decrease both urinary albumin excretion and a progression of nephropathy in patients with diabetic kidney disease. Both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to have these effects [4,7-9].

In the presented study, we observed type 2 diabetic patients with persistent albuminuria on a combination therapy of ACEI/ARB for 12 weeks.

Table 1. Clinical characteristics of the study group - 34 type 2 diabetic patients. The albuminuria results are expressed as median. All other values are expressed as mean \pm SD.

Age (ys)	59 \pm 9
Diabetes duration (ys)	18,6 \pm 12,3
BMI (kg/m ²)	29,35 \pm 5,6
Sex (F/M)	18/16
Serum creatinine (mg/dl)	1,27 \pm 0,39
Total cholesterol (mg/dl)	190,4 \pm 34,2
Triglycerides (mg/dl)	124,5 \pm 55,9
HbA1c (%)	6,7 \pm 0,3
MAP (mmHg)	89,5 \pm 3,2
Albuminuria (mg/24h)	157 mg/24h

MATERIALS AND METHODS

The study population consisted of 34 patients with diabetic nephropathy, who fail to significantly decrease albuminuria on the maximum ACEI dose and dietary protein restriction of < 1 g/kg/day. The angiotensin receptor blocker - telmisartan in a dose of 40 mg, was added to the treatment and the patients were observed for 12 weeks. The characteristic of the study group is provided in *Tab. 1*. All patients received insulin or insulin plus oral hypoglycemic drugs to control diabetes. All patients had been treated for hypertension with ACEI. Enalapril (40 mg/day) was used in 24 patients, perindopril 10 mg/day in 8 patients and lisinopril 20 mg/day in 2 patients. Additional blood lowering medications included: beta-blockers (15 patients) and diuretics (20 patients), which were continued at the same dose when telmisartan was added.

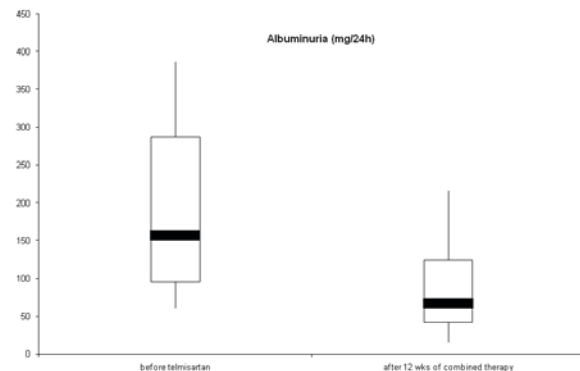
We measured the creatinine clearance, urinary albumin excretion in the 24-hour urine collections, before and after 12 weeks of combined therapy.

Statistical analysis was performed using analysis of variance or Student's *t* test for paired data, as appropriate. The albuminuria results are expressed as median with interquartile range. All other values are expressed as mean \pm SD.

RESULTS

The addition of 20 mg of telmisartan to ACEI therapy resulted in a significant reduction of albuminuria from 157 to 67 mg/24h (*Fig. 1*) in a group of stable patients with type 2 diabetes and persistent albuminuria. No change in creatinine clearance was observed (93 vs 97 ml/min). Blood pressure did not fall significantly during the study (MAP 89,5 \pm 3,2 vs. 88,0 \pm 8,8 mmHg, NS), except in 1 patient who was afflicted by prolonged dizziness and necessitated telmisartan withdrawal. In all others, therapy was generally well tolerated. Transient loose stools were observed in 1 patient in the first week after the addition of telmisartan. Serum potassium was closely

Figure 1. Box Whisker plot (median with quartiles) for albuminuria in 34 type 2 diabetic patients before and after 12 weeks of combined treatment with maximal ACE doses and 40 mg telmisartan.



monitored during the study. No severe hyperkalemia episode occurred. Asymptomatic serum potassium elevation- defined as a serum potassium above 5,5 mmol/l- was found in 4 patients in association with hyperglycemic episodes, and was promptly managed by diet and insulin dose modification.

DISCUSSION

A non-comparative, open-label study was performed, which showed a decrease in albuminuria after adding telmisartan to the combined antihypertensive therapy including ACEI.

Many studies of diabetic subjects and animals suggest that intraglomerular hypertension and glomerular hypertrophy play a vital role by being present early in the disease (as diabetes induces renal vasodilation and often a rise in glomerular filtration rate) and then being exacerbated by the compensatory response to nephron loss. On the other hand, reducing the intraglomerular pressure with dietary protein restriction or antihypertensive therapy with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker can minimize progression of or even prevent glomerular disease in the absence of glycemic control [6,10-12]. Furthermore, ACE inhibition was more effective than other antihypertensive agents, both in lowering the intraglomerular pressure and in minimizing glomerular injury [6, 10]. Thus, the blockade of the rennin-angiotensin system (RAS) is the most important proven strategy to induce regression of renal disease in diabetic nephropathy at functional and structural levels.

The combination of ACEI/ARB has been suggested as a way to maximize RAS blockade because it affects both the bioavailability of angiotensin II and its activity at the receptor level. The superior, long-term renoprotective effect of combined therapy was confirmed in non-diabetic patients [13,14].

The theoretical benefits of combination therapy include those of ACEI, e.g. a decrease in angiotensin II levels via

increased bradykinin and decreased aldosterone production. The addition of ARB may further decrease albuminuria by inhibiting angiotensin II produced by an alternative enzyme, e.g. chymase and increase AT2 receptor activation which may be vasodilatory, antiproliferative and antifibrotic.

Telmisartan is a nonpeptide AT1 angiotensin II receptor antagonist. This binding prevents angiotensin II from binding to the receptor, thereby blocking vasoconstriction and aldosterone secretion effects angiotensin II. Telmisartan has been proved to be not inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes [9]. In this study, it was demonstrated that combination ACEI/ARB therapy is more antiproteinuric than ACEI alone. The addition of telmisartan to routine treatment offered additional albuminuria reduction in patients with diabetic nephropathy. The VAL-HEFT study [15] results suggested that the addition of ARB to beta blocker and ACEI increases mortality. 15 of the patients in our study were on beta blocker therapy during the study. None of them had signs of systolic dysfunction or heart failure. We did not demonstrate any adverse effects of combination therapy in these patients, which confirms the results of the CHARM study [16].

The recently published ONTARGET study [17] compared telmisartan, ramipril and combination therapy with both agents in over 25 000 patients with high cardiovascular risk. Although the achieved mean blood pressure was lower in patients who received telmisartan or both agents compared to ramipril alone, the cardiovascular outcomes were found to be the same as in the monotherapy groups. Moreover, patients treated with combined therapy had a higher rate of adverse events that required drug discontinuation. These included hypotensive symptoms, syncope, and renal impairment, hyperkalemia and an almost significant increase in overall mortality. The ONTARGET study was not primarily a renal protection study and combined therapy did not aim to slow kidney disease progression, but to gain cardiovascular benefits. The telmisartan dose used in combination therapy in the ONTARGET study was 80 mg, which is twice as much as the dose used in our presented study. Added to a maximal ramipril dose, this can explain the large number of hypotensive symptoms. The ONTARGET study population was different than in the presented study. The patients in ONTARGET had documented atherosclerotic vascular disease and diabetes mellitus, but only a small subgroup of them had increased urinary protein excretion – microalbuminuria was found in 13% of patients, macroalbuminuria in 4%. Detailed renal outcomes of the ONTARGET study [18] showed that combination therapy slowed the increase in albuminuria, which is in agreement with our findings, and prevented new onset of micro- and macroalbuminuria. No benefit and potential harm was found in high risk patients with diabetic nephropathy and low eGFR (less than 60 ml/min/1.73m²).

The incidence of hyperkalemia on combination therapy in our study is not different than that reported for therapy with ACEI alone [7,8]. In fact, no increase in kaliemia associated

with telmisartan was noted in our study. All 4 episodes occurred in insulin treated patients, were clearly associated with acute transient hyperglycemic episodes, and were not present when glycemia normalized.

Transient loose stools were observed in one patient in the first week after the addition of telmisartan, with no liver function deterioration or hyperkalemia.

We had to stop telmisartan in one case due to dizziness without a significant drop in blood pressure. This occurred after a few days of treatment and reoccurred after the drug was reintroduced 2 weeks later. The patient started telmisartan at a blood pressure of 120/70 which seems to be his goal blood pressure.

CONCLUSIONS

The addition of telmisartan to a maximum dose of ACEI is safe and results in further albuminuria decrease in patients with type 2 diabetes and incipient nephropathy. An obvious limitation of our study is its non-comparative open-label nature, and therefore bias cannot be excluded. On the other hand, this study describes actual intervention in outpatient clinic settings. Further follow-up of the study population will show if combination of ACEI/ARB is also more renoprotective.

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