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Microalbuminuria and hypertension in HIV-infected patients: a preliminary study of telmisartan

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Abstract. – *Background:* **There is increasing evidence of hypertension and microalbuminuria in HIV-infected patients, and these are two important risk factors for renal and cardiovascular disease. Anti-hypertensive drugs inhibiting the renin-angiotensin system exert an antiproteinuric effect. Telmisartan, an angiotensin II receptor blocker and partial peroxisome proliferator-activated receptor γ (PPAR γ) agonist that is approved for the treatment of hypertension, appears to exert a nephroprotective effect independent of blood pressure reduction in the general population.**

Objective: **The aim of this preliminary study was to evaluate possible nephroprotective effects of telmisartan in hypertensive HIV-positive patients with microalbuminuria.**

Patients and Methods: **Caucasian male patients with HIV infection (n=13) receiving stable combined antiretroviral therapy (without therapeutic changes for > 12 months) and a recent diagnosis of grade 1 hypertension were treated with daily oral telmisartan 80 mg for 6 months. Patients had suppressed viremia and a CD4 cell count > 300 cells/mL for 6 months, and microalbuminuria > 5 mg/dL. Systolic and diastolic blood pressure (SBP, DBP), triglycerides, total cholesterol, HDL cholesterol and LDL cholesterol, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), microalbuminuria, Modification of Diet Renal Disease-Glomerular Filtration Rate (MDRD-GFR), vascular endothelial growth factor (VEGF) and endothelin-1 were measured at baseline and at one, three and six months. All statistical analyses were performed using SAS 9.2.**

Results: **A significant reduction of microalbuminuria ($p < 0.001$) with stable MDRD-GFR was observed, although the main indices of renal function showed no substantial change. A significant reduction in mean SBP and DBP was observed at T1 and confirmed at T3 and T6 (SBP $p < 0.001$ and DBP $p < 0.001$), and there was BP normalization. Metabolic assessments showed an improvement in lipid parameters, and a significant decrease in insulin resistance assessed by the homeostasis model assessment index-insulin resistance (HOMA-IR) ($p = 0.04$).**

In addition, there was a statistically significant reduction in ESR ($p = 0.02$) and a non significant reduction in CRP. Other results included a significant reduction in serum VEGF and endothelin-1 levels ($p < 0.001$).

Conclusions: **From these preliminary findings, telmisartan has demonstrated efficacy in the control of hypertension and microalbuminuria in HIV-infected patients. Decreased microalbuminuria with stable MDRD-GFR may be indicative of a nephroprotective effect of telmisartan; mechanisms causing microalbuminuria in patients with HIV could be related to infection, chronic inflammation, and endothelial dysfunction. The decreased endothelin-1 and VEGF levels in patients in this study may be related to an endothelial protective effect of telmisartan. This study reports the first observation of renal and endothelial protective effects of telmisartan in HIV-positive patients.**

Key Words:

Telmisartan, Kidney disease, Microalbuminuria, HIV infection, VEGF, Endothelin-1.

Introduction

The introduction of combined antiretroviral therapy (cART) has significantly improved survival among patients with HIV over the last decade[1,2]. However, it has also resulted in important short- and long-term adverse effects such as hypertension, diabetes mellitus and dyslipidemia[3,4], which simultaneously contribute to the development and progression of cardiovascular and kidney disease in the setting of HIV infection[5,6]. As a result, chronic kidney disease (CKD) has become an increasingly prevalent complication of HIV infection[7,8], most of which is caused by HIV-associated nephropathy (HIVAN)[7,9]. However, up to 50% of kidney disease in HIV-infected individuals

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results from a wide range of non-HIVAN pathology, ranging from glomerulonephritis to diabetic nephropathy[5]. HIV-associated renal disease with overt proteinuria has been associated with an increased risk of CKD, end-stage renal disease, worse outcomes and increased mortality[10,11]. An increased urinary albumin excretion rate, even in the microalbuminuria range, has been found to be an independent risk factor for cardiovascular disease (CVD) and mortality in the general population[12,13] and in HIV-infected individuals[14,15].

HIV infection shows a strong and independent association with microalbuminuria[16], since, besides the potential nephrotoxicity induced by cART[17], HIV itself may directly affect glomerular epithelial cells[18]. Microalbuminuria is a predictor for the development of proteinuria among HIV-infected patients[19]. These associations suggest that microalbuminuria might be a marker of early and diffuse vascular damage that might affect renal and other outcomes[20]. Endothelial dysfunction has been proposed as a possible cause of microalbuminuria and as a putative link between it, HIV infection and an increased risk of CKD and CVD[21,22].

Recent data demonstrate that blood pressure is a major determinant of albumin excretion in selected and unselected HIV-infected cohorts[16,22]. The prevalence of hypertension in HIV-infected patients ranges from 34% to 55%, and hypertensive patients with HIV infection are more likely to have insulin resistance, metabolic syndrome[23,24], and proteinuria[25]. This underscores the importance of optimizing blood pressure and achieving glycaemia control to minimize the impact of CKD in HIV infection. Anti-hypertensive drugs inhibiting the renin-angiotensin system (RAS) are the drugs of choice for patients with proteinuria[26]. Telmisartan, an angiotensin II receptor 1 (AT1) blocker (ARB) and partial agonist of the peroxisome proliferator-activated receptor γ (PPAR-γ) approved for the treatment of hypertension[27,28], appears to exert a nephroprotective effect in non HIV-infected patients with hypertension, diabetes and CKD[29,30]. Data relating to the effects of sartans in HIV-positive patients are lacking. The aim of this preliminary study was to evaluate the possible nephroprotective effects of telmisartan in hypertensive HIV-infected patients with microalbuminuria.

Patients and Methods

This was an observational study of consecutive outpatients attending the Clinic of Infectious Diseases, SS. Annunziata Hospital, of the "G. d'Annunzio" University of Chieti-Pescara, Italy, from January 2008 to December 2008.

Study Population

Eighty-nine patients were assessed for study eligibility; enrolment criteria included being adult, Caucasian, male, HIV-infection, negative viremia, and microalbuminuria, ≥12 months of cumulative exposure to different antiretroviral regimens, without modification of cART for over 12 months, HIV-RNA levels <40 copies/mL and a CD4 cell count >300 cells/mL for 6 months. In this study, microalbuminuria was defined as a urinary albumin excretion rate greater than 5 mg/dL, determined over three assessments (daily over 3 consecutive days), the first two of which confirmed the presence of protein excretion. The immunonephelometry technique allowed to quickly and simply run the analysis, although the technical limits in the given clinical environment. This technique has been validated for population and first level screening for albumin analysis[31,32].

Exclusion criteria included: refusal to provide informed consent, active use of illicit drugs, microalbuminuria <5 mg/dL confirmed in more than two urine examinations, presence of chronic viral hepatitis or diabetes mellitus and evidence of an acute infection within 3 months of the study, a recent diagnosis of grade 1 hypertension according to European Society of Hypertension criteria[27] and microalbuminuria consistently >5 mg/dL, and antihypertensive agent use.

This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. All subjects gave informed consent for the study and the study was approved by the Ethics Committee of the "G. d'Annunzio" University, School of Medicine.

Patients were treated with oral telmisartan 80 mg daily for 6 months, and asked to adhere to their usual diet and lifestyle during the study.

Height, weight, waist circumference and body mass index (weight in kilograms divided by the square of height in meters) were recorded. Study assessments were recorded at baseline (T0), and at one (T1), three (T3) and six (T6) months. Measurement of blood pressure and heart rate were made in duplicate at baseline and thereafter at each clinic visit >24 h after intake of the study medication. Duplicate measurements were separated by an interval of at least 5 minutes, after the patients had rested in a seated position. Ambulatory blood pressure was measured, to the nearest 2 mmHg, in the same arm

at each visit using a mercury sphygmomanometer (ERKA medical, Bad-Tölz, Germany). Heart rate was measured by pulse palpation for 30 seconds immediately after the blood pressure measurement. The average of the duplicate measurements was used for statistical analysis of systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Biochemical Analysis

A fasting venous blood sample, from the antecubital vein, was collected from all participants at the time of each clinic examination to determine levels of: triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol, fasting glucose, insulin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, urea nitrogen, and uric acid. Routine laboratory tests were performed at the Unit of Clinical Pathology, SS. Annunziata Hospital, Chieti, Italy.

Insulin resistance was determined using the homeostasis model assessment index for insulin resistance (HOMA-IR) with the following formula: (fasting insulin level in micro units per millilitre × glucose level in millimoles per litre)/22.5.

Microalbuminuria was measured on single-day urine samples collected for three consecutive days using particle-enhanced immunonephelometric assays (BN II System, Siemens Healthcare Diagnostics, Inc, Milan, Italy). The mean value of these measurements for each patient was calculated and used.

Glomerular filtration rate (GFR) was assessed using the simplified Modification of Diet Renal Disease (MDRD) logarithmic model, which takes into account levels of plasma creatinine, age, gender and race[8].

Endothelin-1 and vascular endothelial growth factor (VEGF) plasma levels were determined using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) following the manufacturers' recommendations. The minimum detectable dose of endothelin-1 ranged from 0.3-0.9 pg/mL and the range of VEGF determination was from 1.61-5.99 pg/mL.

Virologic and Immunologic Markers

CD4- and CD8-T cell counts were obtained by cytofluorimetric BD FACS CONTO1, San Josè, CA, USA) assessment of lymphocyte subpopulations. Plasma viral load (HIV-RNA) was determined using the "Amplicor" method (Roche Molecular Diagnostics Milan, Italy), with a detection limit >40 copies/mL.

Statistical Analysis

Data are reported as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables.

Differences between variables in study values at baseline, 1 month, 3 months and 6 months were evaluated using a mixed models analysis of covariance (Proc Mixed), to eliminate confounding factors. The advantage of this approach is that it increases the precision of the estimate by using all available information and, at the same time, allows for handling missing data. The *p*-value reported for comparisons between the different study timepoints was Bonferroni-adjusted. Moreover, p-for-trend was also calculated.

Potential confounding of blood pressure control (model 2), markers for endothelial damage (model 3) and inflammation (model 4) were evaluated using covariance mixed models.

A two-tailed p-value ≤ 0.05 was considered significant. Analyses were carried out with statistical package SAS 9.2.

Results

Thirteen of the 89 patients assessed were enrolled in the study and treated with oral telmisartan 80 mg daily for 6 months. The median age was 51 ± 8 years.

All patients had a stable HIV-RNA <40 copies/mL, and constant CD4 cell counts throughout the study (T0: 474 ± 51; T1: 475 ± 54; T3: 481 ± 48; T6: 490 ± 50).

Telmisartan 80 mg daily for 6 months in HIV-infected cART-treated patients with hypertension and microalbuminuria substantially improved kidney function by reducing microalbuminuria levels, in addition to effectively normalizing BP.

Patients showed a significant reduction in microalbuminuria ($p < 0.001$) with stable MDRD-GFR, while the main indices of renal functional showed no substantial change (Table I). Statistically significant reductions in blood pressure were observed at 1 month of treatment and further confirmed at T3 and T6 (SBP $p < 0.001$ and DBP $p < 0.001$), and there was normalization of blood pressure (Table I).

Regarding metabolic parameters, the impaired lipid profile at baseline improved during the study period. In particular, serum levels of total cholesterol ($p < 0.001$), LDL cholesterol ($p < 0.001$) and triglycerides ($p < 0.001$) were decreased, while HDL cholesterol was augmented. With regard to

Table I. Mean values (± standard deviation) for selected measures in patients (n=13) treated with telmisartan for 6 months.

Parameter	Baseline (T0)	1 month (T1)	3 months (T3)	6 months (T6)	*p*
Systolic blood pressure, mmHg	149.62 ± 2.00	136.92 ± 1.65	133.08 ± 2.80	132.31 ± 2.01	< 0.001
Diastolic blood pressure, mmHg	94.23 ± 1.37	84.23 ± 1.59	82.31 ± 1.34	83.08 ± 1.06	< 0.001
Microalbuminuria, mg/dL	12.50 ± 2.06	7.43 ± 1.28	5.02 ± 0.77	3.93 ± 0.75	< 0.001
MDRD GFR, mL/min/1.73 m^2	81.92 ± 4.34	82.00 ± 4.62	88.77 ± 7.52	83.38 ± 4.40	0.10
Creatinine, mg/dL	1.02 ± 0.05	1.02 ± 0.06	0.99 ± 0.06	1.02 ± 0.05	0.26
BUN, mg/dL	17.92 ± 1.13	18.77 ± 1.36	16.92 ± 1.23	18.69 ± 1.46	0.49
Uric acid, mg/dL	5.86 ± 0.20	5.99 ± 0.25	6.06 ± 0.32	6.26 ± 0.33	0.32
Total cholesterol, mg/dL	225.85 ± 10.74	228.54 ± 10.91	216.92 ± 11.22	209.15 ± 11.52	< 0.001
HDL-cholesterol, mg/mL	40.69 ± 2.41	42.31 ± 3.18	43.69 ± 2.76	43.46 ± 2.48	0.13
LDL- cholesterol, mg/dL	133.85 ± 9.69	140.20 ± 9.40	127.62 ± 9.45	122.66 ± 10.26	< 0.001
Triglycerides, mg/mL	260.08 ± 27.64	224.46 ± 21.67	213.23 ± 22.28	219.54 ± 21.67	< 0.001
HOMA-IR	3.13 ± 0.49	2.90 ± 0.46	2.91 ± 0.47	2.78 ± 0.40	0.04
ESR, mm/h	18.62 ± 3.59	14.85 ± 2.74	13.85 ± 1.98	12.38 ± 2.41	0.02
C reactive protein , mg/dL	0.47 ± 0.04	0.55 ± 0.13	0.57 ± 0.09	0.38 ± 0.04	0.32
Endothelin-1, pg/mL	16.44 ± 0.77	15.72 ± 0.73	15.24 ± 0.77	15.00 ± 0.77	< 0.001
VEGF, pg/dL	461.76 ± 40.82	413.53 ± 39.31	383.67 ± 37.01	373.97 ± 35.88	< 0.001

BUN = blood urea nitrogen; ESR = erythrocyte sedimentation rate; GFR = glomerular filtration rate; HDL = high density lipoprotein; HOMA-IR = homeostasis model assessment index - insulin resistance; LDL = low density lipoprotein; MDRD = Modification of Diet Renal Disease; VEGF = vascular endothelial growth factor.

carbohydrate metabolism, although fasting glucose levels were not significantly altered throughout the study, a significant decrease in HOMA-IR levels was observed ($p = 0.04$) (Table I).

Telmisartan also demonstrated an anti-inflammatory effect, with a statistically significant reduction in ESR ($p = 0.02$) and a non significant reduction of CRP. A significant reduction of serum VEGF and endothelin-1 levels was also detected ($p < 0.001$) (Table I).

In further analyses of the reduction of microalbuminuria during telmisartan treatment, it was observed that adjusting for different models and, in particular, model 2 (adjusting for changes in SBP and DBP), there was a decrease in the difference in time for which microalbuminuria existed. Adjusting the model further, for changes in VEGF and ESR (models 3 and 4), this difference increased. Despite these various model adjustments, microalbuminuria continued to decline significantly over time (Table II).

There were no adverse events, including gastrointestinal disturbances, or drop-outs during the study treatment, and study compliance was absolute.

Discussion

The main findings of this study are that a 6-month course of telmisartan 80 mg daily in HIV-infected cART-treated patients with hypertension

Table II. Mean (± standard error) microalbuminuria levels (mg/dL) in patients (n=13) receiving telmisartan for 6 months, and adjusted according to different models (*p* values vs baseline).

	Baseline (T0) Mean ± SE	1 month (T1) Mean ± SE	*p*-value	3 months (T3) Mean ± SE	*p*-value	6 months (T6) Mean ± SE	*p*-value
Model 1	12.5 ± 1.3	7.4 ± 1.3	0.003	5.0 ± 1.3	< 0.001	3.9 ± 1.3	< 0.001
Model 2	12.0 ± 1.9	7.4 ± 1.3	0.20	5.2 ± 1.4	0.04	4.3 ± 1.4	0.02
Model 3	12.2 ± 2.1	7.4 ± 1.4	0.21	5.1 ± 1.5	0.06	4.1 ± 1.5	0.02
Model 4	11.7 ± 1.9	7.3 ± 1.3	0.24	5.3 ± 1.4	0.06	5.4 ± 1.4	0.03

Model 1: crude values for the changes in microalbuminuria over the different phases of the study. *Model 2:* microalbuminuria values adjusted for changes in systolic (SBP) and diastolic blood pressure (DBP) during the different phases of the study. *Model 3:* microalbuminuria values adjusted for changes in SBP, DBP, and vascular endothelial growth factor (VEGF) serum levels during the different phases of the study. *Model 4:* microalbuminuria values adjusted for changes in SBP, DBP, VEGF and erythrocyte sedimentation rate (ESR) serum levels during the different phases of the study.

and microalbuminuria substantially improved kidney function by reducing microalbuminuria levels, in addition to effectively normalizing BP.

Telmisartan improved microalbuminuria in the study population despite not significantly improving GFR. The recently published "ONgoing Telmisartan Alone and in combination with Ramipril Global End-point Trial" (ONTARGET) has shown that in patients at high vascular risk, the effects of telmisartan on major renal outcomes are similar, and non-inferior, to those of ramipril[33]. Furthermore, several studies have reported a favourable effect of telmisartan on renal disease in hypertensive subjects, with or without diabetes and CKD, in the general population[30,34-36]. The findings of the present study support this evidence and show that telmisartan may also exert a nephroprotective effect in HIV-positive cART-treated patients.

Hypertension is closely related to the development of CKD. Microalbuminuria and proteinuria are also features of hypertensive renal damage. In turn, renal disease has been associated with CVD, and increased morbidity and mortality[37]. Adequate BP control ameliorates the progression of renal damage. In the present study, telmisartan was rapidly efficacious in significantly reducing both SBP and DBP after 1 month of treatment, and normalizing BP values at 6 months. These findings confirm the anti-hypertensive efficacy of telmisartan in HIV-infected patients treated with cART and indicate that telmisartan may play a pivotal role in preventing renal damage, as previously suggested[38].

Furthermore, telmisartan demonstrated beneficial effects on the lipid profile and glucose metabolism in this patient population, in line with other evidence[39]. This finding is in keeping with previous data in a non-HIV-infected population[40,41]. These effects may stem from effective activation of PPAR-γ and not just on AT1 receptor blockade, since PPAR-γ regulates a plethora of genes that are related to metabolic parameters[42]. Therefore, by improving insulin resistance and lipids, which are associated with CKD progression[43], telmisartan may have additive beneficial effects on renal function.

Since HIV infection is associated with an inflammatory activation in the vascular wall which may promote glomerular damage, this study sought to evaluate the potential influence of telmisartan on systemic inflammation and endothelial dysfunction in HIV-infected patients. Telmisartan has previously been shown to demonstrate anti-inflammatory and anti-oxidant properties against oxidative damage both in non-infected endothelial cells in *in vitro* experiments and in *in vivo* models[44,45]. The current study demonstrated an anti-inflammatory effect for telmisartan, as indicated by significant reductions in the principal inflammatory index.

Another interesting result in this study is that telmisartan significantly reduced endothelin-1 and VEGF levels. Endothelin-1 is a potent vasoconstrictor, pro-inflammatory and mitogenic peptide, which is produced by endothelial and inflammatory cell types[46], and is important for maintaining vascular tone. An increase in its production and biological activity are important features of endothelial dysfunction, an early event in the development of atherosclerosis associated with increased cardiovascular risk[47,48]. PPARγ ligands have been demonstrated to inhibit cytokine-mediated endothelial cell proliferation, and to suppress endothelin-1 secretion from vascular endothelial cells both *in vitro* and in humans with diabetes mellitus, microalbuminuria and the metabolic syndrome[49-51]. The results of this investigation study are in agreement with this evidence, as telmisartan reduced endothelin-1 serum levels in HIV-infected patients with hypertension and microalbuminuria. There is, however, no indication as to whether these effects are related to direct PPARγ activation or the indirect consequence of decreased insulin resistance, since several findings support the role of insulin in regulating endothelin-1 levels[52].

VEGF is an angiogenic mitogen, which also increases vascular permeability in a wide range of organs[53]. Elevated VEGF plasma levels have been shown in the presence of hypertension, myocardial ischemia and hyperglycaemia, and are associated with the occurrence of microalbuminuria in diabetic subjects[54-56]. It has been proposed that elevated VEGF levels may be the link between cardiovascular risk factors and vascular injury such as microalbuminuria[56].

Data in HIV-infected populations are lacking. The mechanisms underlying the regulation of endothelial function in HIV-infected patients are not well elucidated, but are likely multifactorial, including direct effects of HIV on endothelial cells, indirect effects of HIV on lipid and pro-inflammatory processes, cART-related metabolic derangements, and traditional/host factors. It is notable that the HIV-positive patients with hypertension and microalbuminuria evaluated in this trial showed initially high VEGF levels, which later decreased with the use of telmisartan. Therefore, it may be hypothesized that telmisartan exerts endothelial protective effects.

The beneficial effects of telmisartan on renal function may be mediated by various mechanisms. The reduction of microalbuminuria throughout the study period seems to be initially associated with the antihypertensive effect of telmisartan, since it was not significantly decreased at T1 in models 2, 3 and 4. On the other hand, reduced microalbuminuria seems to be independent of successive BP reduction. These findings are in keeping with the results of other studies showing that the effect of telmisartan in reducing urine albumin excretion may extend beyond BP lowering[57]. Thus, the mechanism by which telmisartan reduced microalbuminuria in our HIV-infected patients may be linked not only to its action on hemodynamic factors, but also to its anti-inflammatory and endothelium protective abilities, as showed by reduced ERS and VEGF levels. In fact, telmisartan, like all ARBs, blocks the adverse effects of angiotensin II in the kidneys, such as proinflammatory effects, oxidative stress and promotion of cell growth and fibrosis[58].

Finally, telmisartan seems to have no direct effect on HIV replication and immunological parameters. In particular, telmisartan does not appear to interfere with cART, although further studies in this context are warranted.

One of the main limitations of this study is its purely observational nature, with the lack of one or more parallel control arms, which, in future studies, should include structurally unrelated ARBs, without PPARγ-activating properties. Another limitation is the relatively small number of patients that were evaluated, as a result of the strict selection criteria. In order to minimize the possible direct impact of HIV on endothelial cells through active viral replication, only patients with HIV-RNA <40 copies/mL were included. These limitations warrant further studies to confirm these initial observations.

Conclusions

Telmisartan is safe, well-tolerated and effective for the control of hypertension and microalbuminuria in HIV-infected patients. The drug demonstrates renal protective effects, as shown by the decrease in microalbuminuria, and anti-inflammatory and endothelial protective properties, as indicated by reductions in ESR, endothelin-1 and VEGF. Further studies are needed to confirm these initial observations.

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