Original Paper

Telmisartan Effects on Insulin Resistance in Obese or Overweight Adults Without Diabetes or Hypertension

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Angiotensin receptor blockers (ARBs) are antihypertensive agents associated with reduced risk of new-onset diabetes mellitus. The ARB telmisartan is a partial agonist of peroxisome proliferator–activated receptor-gamma (PPAR-γ). This study evaluated the effect of telmisartan on insulin resistance, a known target of PPAR-γ agonism. Overweight/obese persons with body mass index ≥28 kg/m^2, waist circumference ≥35 inches, and components of the metabolic syndrome without hypertension or diabetes who were not preselected for insulin resistance were enrolled. Patients were randomized to telmisartan or matching placebo for 16 weeks. The primary efficacy measure was changed from baseline in the insulin sensitivity index (SI), calculated from oral glucose tolerance testing. SI was also evaluated in a subset of patients using a hyperinsulinemic euglycemic clamp. Secondary end points included measures of insulin sensitivity and glucose and lipid metabolism. A total of 138 patients were randomized and received ≥1 dose of study medication; 128 completed the study. At end point, no significant difference was found between telmisartan and placebo groups regarding change from baseline in SI or in glucose area under the curve. No significant between-group differences were found regarding glucose metabolism or lipoprotein levels. In the population with abdominal obesity and components of the metabolic syndrome, telmisartan did not increase insulin sensitivity.
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Angiotensin II receptor antagonists (angiotensin receptor blockers [ARBs]) are widely used clinically as antihypertensive agents. In addition to reducing blood pressure (BP), ARBs attenuate cardiovascular risk via suppression of the renin-angiotensin system (RAS) mediated by antagonism of the angiotensin II (AT_1) receptor.[1] Studies demonstrate that ARBs not only reduce the risk of cardiovascular events but are also associated with regression of target organ damage secondary to RAS activation, including left ventricular hypertrophy, congestive heart failure, and nephropathy.

ARBs are also associated with a reduced incidence of new-onset diabetes mellitus (DM). In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study,[2] risk of new-onset DM was 25% lower among patients receiving losartan vs those receiving the β-blocker atenolol (95% confidence interval [CI], 12%–37%; $P<.001$). In the Ongoing Telmisartan Alone and in Combination

With Ramipril Global Endpoint Trial (ONTARGET),[3] the rate of new-onset DM was similar with telmisartan and the angiotensin-converting enzyme inhibitor ramipril (odds ratio, 1.12; 95% CI, 0.97–1.29). A meta-analysis of 5 studies showed that ARBs significantly reduced the incidence of new-onset DM among potential high-risk nondiabetic patients vs placebo (odds ratio, 0.76; 95% CI, 0.70–0.82).[4]

Preclinical studies show that telmisartan is a partial agonist of peroxisome proliferator–activated receptor-gamma (PPAR-γ), a ligand-activated nuclear receptor involved in the regulation of aspects of lipid and carbohydrate metabolism.[5] Activation of PPAR-γ is recognized as a principal activity of the thiazolidinedione class of insulin-sensitizing oral antidiabetic drugs, which includes pioglitazone and rosiglitazone.[6] Telmisartan shares structural homology with pioglitazone, and in vitro studies show that it is a selective partial agonist of PPAR-γ of moderate potency (approximately 25%–30% of pioglitazone activity) and no PPAR-α or PPAR-δ activity.[5,7]

PPAR-γ agonism appears specific to telmisartan rather than to a class effect of ARBs. Studies comparing telmisartan with other ARBs demonstrate greater effects for telmisartan on glucose and lipid metabolism, including reductions in measures of insulin resistance (IR) (fasting plasma glucose [FPG], fasting plasma insulin [FPI], glycosylated hemoglobin [HbA_{1c}], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TG]; $P<.05$ for all comparisons).[8,9] In one study, hypertensive patients with type 2 DM and poor glucose control achieved improved insulin sensitivity and reduced HbA_{1c} after being switched to telmisartan from stable treatment with other ARBs.[10]

Because of the potential of telmisartan to mediate IR, also via effects on PPAR-γ, we conducted a study of its effects on parameters of IR in overweight or obese insulin-resistant patients. The study was conducted with normotensive individuals to help discern metabolic effects from those possibly related to BP reduction. Further, patients were required to be nondiabetic at baseline to eliminate confounding effects of antidiabetic medications on IR. Patients were considered to be insulin resistant and at elevated risk for DM or the metabolic syndrome (MetS) if they were obese or overweight and had components of MetS.

DESIGN/METHODS

This phase II, prospective, randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept study was conducted in the United States (8 centers), Canada (4), Germany (3), Italy (2), and Denmark (1) in accordance with the Declaration of Helsinki and the International Conference on Harmonised Tripartite Guideline for Good Clinical Practice Study. Protocols were approved by the applicable institutional review board or ethics committee, and the study is registered at ClinicalTrials.gov (NCT00146289).

Patients

Participants (age 18–65 years) were enrolled with a targeted enrollment of 120. Entry criteria included obese or overweight (body mass index [BMI] $\geq$28 kg/m^2); sedentary lifestyle (not engaging in vigorous activity >30 min/d, for >2 times weekly); waist circumference $\geq$40 in (102 cm) in men or $\geq$35 in (89 cm) in women; nondiabetic (HbA_{1c} $\leq$6.5%, FPG $\leq$126 mg/dL); TG $\geq$150 mg/dL and $\leq$500 mg/dL; and normotensive (BP $\geq$110/64 and $\leq$140/90 mg/dL).

Persons taking antihypertensive medication, DM medications, medications known to alter insulin sensitivity (eg, statins), steroids, glucocorticoids, niacin, nicotinic acid, antipsychotic/antidepressant drugs, or other drugs (including over-the-counter and herbal preparations) known to affect metabolic function were excluded to isolate the effect of telmisartan. Patients were not stratified by IR.

Treatments

Patients meeting inclusion/exclusion criteria were randomized in a 1:1 manner to receive either telmisartan (80 mg/d for 2 weeks, then uptitrated to 160 mg/d for 14 weeks) or matched placebo during the 16-week, double-blind study period. Blinding consisted of 1 tablet of 80-mg telmisartan and 1 tablet of matching placebo once daily for the initial 2 weeks, followed by 2 tablets of telmisartan 80 mg or 2 tablets of placebo once daily for 14 weeks. Compliance was monitored via pill counts and assessment of plasma direct renin levels, which were not reported until study end to maintain blinding. Patients were instructed to maintain constant weight, exercise levels, and eating habits during the study.

Outcome Measures

Efficacy. The study was designed to evaluate whether treatment with telmisartan would increase insulin sensitivity. Patients were assessed using a 3-hour oral glucose tolerance test (OGTT). In addition, a subset of approximately 32 patients was assessed using a 5-hour, 2-step (low-dose insulin infusion: 60 mU/m^2/min; high-dose insulin

infusion: 120 mU/m^2/min) hyperinsulinemic euglycemic clamp procedure. The primary efficacy variable was the adjusted mean change from baseline to study end in the insulin sensitivity index (SI), calculated as the composite index (SI[composite]) from the OGTT.[11] Secondary efficacy variables included changes from baseline to end point in FPG and serum insulin and various measures of glucose and insulin sensitivity (using OGTT and clamp procedures) and changes in circulating levels of inflammatory markers (adiponectin and high-sensitivity C-reactive protein [CRP]) and lipids/lipoproteins (TG, TC, LDL-C, high-density lipoprotein cholesterol [HDL-C], free fatty acids). OGTT assessments included insulin secretion capacity using C-peptide ($\Delta_{0–30\ min}$), area under the curve (AUC) for insulin and glucose, and ratio of $AUC_{glucose}$ divided by $AUC_{insulin}$. Hyperinsulinemic euglycemic clamp procedure assessments included glucose disposal rate (GDR), calculated as the mean glucose infusion rate required to maintain euglycemia during the final 30 minutes of high- and low-dose insulin infusions, and insulin SI, calculated as the ratio of GDR to circulating insulin level.

Safety. Safety was assessed by report of adverse events (AEs). Physical examination and laboratory and electrocardiography (ECG) studies were conducted at baseline and study end and assessed for changes. BP and pulse rate were monitored at each study visit.

Sample Size and Randomization

Evidence indicates that a 20% increase in the insulin SI may be clinically meaningful. There are limited data on use of OGTT to generate this index; therefore, it was not possible to reliably power the study to detect a 20% improvement. A sample size of 50 evaluable patients per group was considered sufficient to estimate the magnitude of a telmisartan treatment effect vs placebo. In addition, a sample size of 15 patients per arm in the hyperinsulinemic euglycemic clamp subgroup was deemed sufficient to detect statistically significant differences between study arms.

The randomization schedule used a validated system employing a pseudorandom number generator to produce a schedule (in a 1:1 ratio with a block size of 4) that was reproducible and nonpredictable. Access to the randomization schedule was restricted to the pharmaceutics department and clinical trial support staff (who generated the randomization code/labels and packaged the clinical supplies); persons directly involved in study conduct and/or analysis had no access to treatment allocation until database lock after completion of the clinical phase.

Data Analysis

Baseline demographics and disease data were summarized for each treatment group and overall. Analysis for primary and secondary efficacy variables was planned using a 2-sided Wilcoxon rank sum test stratified by center at an α level (type I error rate) of 0.05. Regarding the primary efficacy variable, rejection of the null hypothesis would show that telmisartan and placebo differed in their effect on the OGTT insulin SI. Based on methods to evaluate effects on insulin sensitivity, however, it was decided that statistical analysis of the primary end point should instead use analysis of covariance (ANCOVA). ANCOVA was also used for secondary testing of the primary end point and for testing of all secondary end points. The analysis using a 2-sided Wilcoxon rank sum test stratified by center was retained for the primary end point, and the insulin SI (low- and high-dose) was assessed using the clamp procedure.

Because this was a proof-of-concept study, the primary analysis was on a per-protocol (PP) analysis set, comprising all patients without significant protocol violations relevant to the primary efficacy end point. Secondary end points were analyzed using the full analysis set (FAS), comprising all randomized patients.

Planned analyses (on the PP set) used ANCOVA to evaluate any treatment effects on insulin SIs based on the OGTT and clamp procedure in the following predefined patient subgroups: patients with baseline SI(Composite) <2, ≥ 2, or <3; patients with baseline low-dose GDR $<$median value or $\geq$median value (median value was determined to be 3.82); and patients with baseline high-dose GDR $<$median value or $\geq$median value (median value was determined to be 7.425). Patients were excluded from these subgroup analyses if they had questionable OGTT results based on derivation of standard error of the mean (SE) (MinModel).

Additional subgroup analyses were conducted on patients who did not undergo weight change from baseline to study end of $\geq 3\%$ (which might have affected insulin sensitivity) and excluded patients treated with telmisartan who demonstrated a reduction or little change in direct renin (which suggested noncompliance with telmisartan).

Safety analysis was conducted on all patients who received ≥ 1 dose of study drug. Descriptive

Table I. Baseline Demographic, Physical, and Laboratory Parameters (All Randomized Patients)

Parameter	Treatment Group		
	Placebo (n=69)	Telmisartan (n=69)	Overall (N=138)
Mean age, y (SD)	45.2 (11.7)	43.3 (11.9)	44.2 (11.8)
Men, %	62.3	53.6	58.0
Mean weight, kg (SD)	105.5 (24.1)	103.8 (19.7)	104.7 (21.9)
Mean BMI, kg/m^2 (SD)	35.26 (5.26)	35.36 (5.54)	35.31 (5.38)
Mean waist circumference, cm (SD)	112.33 (13.68)	112.16 (14.02)	112.20 (13.80)
Mean HbA_{1c}, % (SD)	5.5 (0.4)	5.5 (0.4)	5.5 (0.4)
Mean HDL-C, mg/dL (SD)[a]	44.7 (12.3)	42.4 (9.9)	
Mean LDL-C, mg/dL (SD)[b]	128.0 (36.2)	128.4 (38.7)	
Mean TG, mg/dL (SD)	229.9 (93.9)	221.9 (99.7)	225.9 (96.5)
Mean systolic BP, mm Hg (SD)	124.6 (8.0)	122.8 (9.3)	123.7 (8.7)
Mean diastolic BP, mm Hg (SD)	78.5 (6.2)	77.1 (7.4)	77.8 (6.8)

Abbreviations: BP, blood pressure; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; SD, standard deviation; TG, trigylcerides. [a]Based on full analysis set (FAS); placebo (n=64) and telmisartan (n=63). [b]Based on FAS; placebo (n=60) and telmisartan (n=55).

statistics were developed for AEs, AEs leading to discontinuation, AEs by severity, and serious AEs. Clinically significant changes from baseline to end point for BP, pulse rate, ECG findings, and physical examination and laboratory results were also evaluated.

RESULTS

A total of 308 participants were enrolled, 138 of whom met the inclusion/exclusion criteria and were randomized to receive study drug (69 patients each for the telmisartan and placebo groups). The most common reasons for exclusion were failure to meet TG inclusion criteria and use of prohibited concomitant therapy.

Of the randomized patients, 128 completed the study (64 per treatment group). Ten patients (7.2%) discontinued after receiving $\geq$1 dose of study drug (5 [7.2%] from each group); 5 patients (3.6%) discontinued because of AEs (2 [2.9%] in the placebo group and 3 [4.3%] in the telmisartan group); and 5 were lost to follow-up (3 [4.3%] in the placebo group and 2 [2.9%] in the telmisartan group).

Table I shows baseline demographic, physical, and laboratory data. Treatment groups were well matched for baseline age, weight, BMI, and other physical and laboratory parameters. There were slightly more men in the placebo group (43 [62.3%]) than in the telmisartan group (37 [53.6%]). Approximately 95% of patients in both groups were white.

Table II summarizes treatment group means at baseline and end point and adjusted mean changes from baseline for the primary and selected secondary efficacy variables. Regarding the primary efficacy variable, change from baseline to end point in SI(Composite) based on 3-hour OGTT, adjusted mean change (SE) was 0.30 (0.324) in the placebo group and 0.19 (0.356) in the telmisartan group; there was no significant difference between groups (difference, −0.11; P=.8217).

There were no significant between-group differences regarding change from baseline to end point in FPG, fasting serum insulin, insulin secretion capacity (C-peptide), $AUC_{glucose}$, $AUC_{insulin}$, or the $AUC_{glucose}/AUC_{insulin}$ ratio. Similarly, there were no differences between groups regarding changes in serum lipids or inflammatory markers (high-sensitivity CRP or adiponectin).

Variables assessed using the hyperinsulinemic euglycemic glucose clamp procedure (with analyses based on both PP and FAS), including GDR and insulin SI [IS(Clamp) = GDR/I] also demonstrated no significant differences between groups regarding change from baseline to end point. Table III summarizes observed treatment group mean baseline and final IS(Clamp) and GDR values and adjusted mean changes from baseline, for the low- and high-dose conditions.

Regarding the planned subgroup analyses, there were no differences between treatment groups within subgroups predefined according to baseline SI(Composite), baseline low-dose GDR, or baseline high-dose GDR for any primary or secondary efficacy end points (data not shown).

Although not evaluated as a secondary end point, reduction of BP between the active and placebo groups was measured throughout the study. Patients receiving telmisartan had a 6.7% change in

Table II. Observed Values and Change From Baseline in Selected Efficacy Measures (OGTT)

	Observed Values, Mean (SD)				Adjusted Mean Change (SE) From Baseline[a]			
	Placebo		Telmisartan					
Efficacy Variable ($N_{placebo}/N_{telmisartan}$)	Baseline	Final	Baseline	Final	Placebo	Telmisartan	Δ^b	*P* Value
SI(Composite) from OGTT[c] (48/42)	3.16 (1.76)	3.52 (2.42)	3.25 (1.93)	3.55 (2.93)	0.30 (0.324)	0.19 (0.356)	−0.11	.8217
FPG, mg/dL (64/64)	101.21 (13.85)	102.58 (12.70)	99.24 (14.51)	102.17 (12.26)	1.57 (1.091)	2.08 (1.115)	0.52	.7321
Fasting serum insulin, μU/mL (61/63)	16.42 (11.75)	15.64 (11.17)	16.50 (10.64)	17.21 (11.21)	−0.61 (1.241)	0.99 (1.252)	1.60	.3454
C-peptide (0–30 min), ng/mL (61/63)	2.86 (2.30)	2.92 (2.37)	3.24 (2.60)	3.82 (3.00)	0.01 (0.259)	0.63 (0.261)	0.62	.0826
$AUC_{glucose}$, μg h/mL (62/61)	25.191 (5465)	25.686 (5548)	24.456 (4995)	25.672 (5824)	492 (494.1)	938 (514.3)	446	.5193
$AUC_{insulin}$, μg h/mL (57/59)	15.098 (9285)	13.433 (7897)	14.876 (7452)	15.359 (9328)	−1479 (865.4)	670 (881.8)	2148	.0727
Ratio $AUC_{glucose}/AUC_{insulin}$ (56/57)	2.02 (0.90)	2.32 (1.12)	2.08 (1.18)	2.22 (1.44)	0.26 (0.142)	0.12 (0.147)	−0.14	.4704

Abbreviations: AUC, area under the curve; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; SD, standard deviation; SE, standard error of the mean. [a]Model including main effects of treatment and center with baseline as a covariate. [b]Telmisartan group minus placebo group. [c]Primary efficacy variable, based on PP analysis group.

Table III. Insulin SI and GDR (Hyperinsulinemic Euglycemic Clamp)

	Observed Values, Mean (SD)				Adjusted Mean Change (SE) From Baseline[a]			
Variable	Placebo		Telmisartan					
$N_{placebo}/N_{telmisartan}$	Baseline	Final	Baseline	Final	Placebo	Telmisartan	Δ^b	*P* Value
SI(Clamp), mg/kg min per μU/mL[c]								
Low-dose insulin ($60\ mU/m^2/min$) (14/12)	0.0671 (0.0472)	0.0672 (0.0453)	0.0631 (0.0426)	0.0563 (0.0315)	0.0011 (0.00886)	−0.0073 (0.01014)	−0.0084	.5304
High-dose insulin ($120\ mU/m^2/min$) (14/12)	0.0544 (0.0470)	0.0507 (0.0290)	0.0456 (0.0200)	0.0482 (0.0207)	−0.0010 (0.00646)	−0.0017 (0.00750)	−0.0007	.9467
GDR, mg/kg min[d]								
Low-dose insulin ($60\ mU/m^2/min$) (14/13)	4.23 (2.04)	4.69 (1.98)	4.75 (2.73)	4.61 (1.89)	0.39 (0.351)	0.04 (0.376)	−0.35	.4977
High-dose insulin ($120\ mU/m^2/min$) (14/13)	6.75 (3.48)	7.60 (2.31)	7.72 (3.16)	8.18 (2.09)	0.60 (0.425)	0.69 (0.453)	0.10	.8774

Abbreviations: GDR, glucose disposal rate; SD, standard deviation; SE, standard error of the mean; SI, sensitivity index. [a]Model including main effects of treatment and center with baseline as a covariate. [b]Telmisartan group minus placebo group. [c]Results from PP dataset. [d]Results from FAS.

systolic BP vs a 0.5% in the placebo group. A 6.6% change in diastolic BP was seen in the telmisartan group vs 0.9% in the placebo group.

Regarding safety, 61 (44.2%) of 138 randomized patients reported ≥1 AEs during the study. The incidence of AEs was similar between treatment groups: AEs were reported by 32 of 69 patients (46.4%) from the placebo group, 8 of 69 patients (11.6%) from the telmisartan group during the 2-week standard-dose (80 mg/d) phase, and 25 of 68 patients (36.8%) from the telmisartan group during the 14-week high-dose (160 mg/d) phase. The incidence of AEs considered by investigators to be drug-related was also similar between groups (7 [10.1%] in the placebo group and 8 [11.6%] in the telmisartan group), as was the rate of discontinuation due to AEs (placebo, 2.9%; telmisartan, 4.3%).

One patient (in the telmisartan group) reported 2 serious AEs (pneumonia and diarrhea). These were not considered related to study drug; the patient recovered from both AEs and subsequently discontinued participation.

DISCUSSION

This study demonstrated that telmisartan, relative to placebo, was well tolerated in this population at a dose level twice that normally prescribed for treatment of hypertension. However, telmisartan failed to demonstrate significant beneficial effects on parameters of insulin sensitivity and glucose metabolism in a population of normotensive, nondiabetic patients with clinical evidence of IR. This could have been secondary to the fact that there was no stratification to insulin-resistant patients or that the available methodology was not sensitive enough to detect small, subclinical effect.

Patients were enrolled based on abdominal obesity, elevated TG levels, and sedentary lifestyle and thus at significant risk for IR, which is considered an underlying characteristic of MetS. Obesity and TG levels >150 mg/dL are 2 of 5 criterion components of MetS according to the National Cholesterol Education Program definition; patients with ≥3 components are considered to have MetS.[12] In this population, mean values for FPG and HDL-C, 2 other MetS components, suggest that a significant proportion of patients may have had ≥1 additional component and thus crossed the diagnostic threshold for MetS. Although laboratory-confirmed IR (ie, elevated plasma insulin levels or reduced GDR) was not an inclusion criterion, post hoc analysis limited to patients with elevated baseline plasma insulin levels and GDR also failed to demonstrate beneficial effects of telmisartan treatment relative to placebo on either insulin sensitivity or glucose metabolism.

Noteworthy is that given the parameters of the study population at baseline regarding measures of IR and glucose metabolism (including standard deviations as well as mean values), these patients probably exhibited a wide range of insulin sensitivity. The importance of this diversity on the study results is unknown; however, subgroup analysis according to baseline IR has not demonstrated any difference between telmisartan and placebo in the moderate and severe IR groups.

The results of this study do not eliminate the possibility that telmisartan may exert a positive impact on glucose metabolism via mechanisms other than PPAR-γ agonism. Nor do they unequivocally exclude PPAR-γ agonism as a contributing mechanism to positive effects of telmisartan on FPG, FPI, and serum lipoproteins observed in studies that enrolled patients with DM, hypertension, and/or MetS.[8–10] The results, derived using an established sensitive model of IR, including the hyperinsulinemic euglycemic pump (considered the gold standard for insulin sensitivity), suggest that effects of telmisartan on IR or other diabetic parameters probably cannot be attributed to a significant degree to its partial agonistic action on PPAR-γ.

"Isolated" IR (in the absence of hypertension or glucose intolerance) is an important emerging therapeutic target, as shown in a study in which thiazolidinedione treatment reversed coronary vasomotor derangements in a population of insulin-resistant adults without glucose intolerance or other cardiac risk factors.[13] Therefore, studies to characterize the potential effect of partial PPAR agonists, such as telmisartan, on glucose and lipid metabolism, are warranted. Further, studies should be initiated to clarify the underlying beneficial metabolic effects of telmisartan, independent of its partial PPAR agonism effect.

CONCLUSIONS

Telmisartan (160 mg/d) was well tolerated in this population of normotensive, nondiabetic patients; however, telmisartan did not show significant effect on insulin sensitivity. Additional studies of telmisartan in a range of populations may help better characterize its impact on glucose and lipid metabolism and on possible contributory mechanisms.

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