ORIGINAL ARTICLE

Metabolic effects of telmisartan and irbesartan in type 2 diabetic patients with metabolic syndrome treated with rosiglitazone

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SUMMARY

Background and objective: Angiotensin II receptor blockers represent a class of effective and well-tolerated orally active antihypertensive drugs in the general hypertensive population and in diabetic patients. The aim of our study was to investigate the metabolic effects of telmisartan and irbesartan in diabetic subjects treated with rosiglitazone.

Methods: We evaluated 188 type 2 diabetic patients with metabolic syndrome. All patients took a fixed dose of 4 mg rosiglitazone/day. We administered 40 mg telmisartan/day or 150 mg irbesartan/day and evaluated their body mass index, glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment-index (Homa-IR), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, adiponectin and resistin during 12 months of this treatment.

Results and discussion: In addition to a comparable antihypertensive effect for telmisartan and irbesartan after 6 and 12 months, both treatments were associated with a significant reduction in TC and LDL-C plasma levels compared with baseline. After 6 months of treatment, only the telmisartan group experienced a significant improvement in (HbA1c), FPG, Homa-IR, adiponectin and resistin compared with the baseline values, whereas both drug regimens were associated with a significant improvement in these parameters after 12 months. However, the improvements observed in the telmisartan group were significantly larger than that noted in the irbesartan group after 12 months of treatment. FPI significantly decreased only after 12 months of treatment in both groups, but again, the reduction was significantly larger in the telmisartan-treated subjects.

Conclusions: Telmisartan seemed to improve glycaemic and lipid control and metabolic parameters of the metabolic syndrome better than irbesartan. These differences could be relevant in the choice of therapy for this condition and diabetes.

Keywords: irbesartan, metabolic syndrome, rosiglitazone, telmisartan, type 2 diabetes

INTRODUCTION

Even modest increases in blood pressure (BP) are associated with an increased risk of cardiovascular complications in diabetes mellitus (DM). Large trials and meta-analyses have shown that treatment with BP-lowering agents in type 2 diabetes significantly lowers the risk of cardiovascular and microvascular complications (1). Angiotensin II receptor blockers represent a class of effective and well-tolerated orally active antihypertensive drugs both in the general hypertensive population and in
diabetic patients (2). Activation of angiotensin II type 1 [AT(1)] receptors leads to vasoconstriction, stimulation of the release of catecholamines and antidiuretic hormone and promotion of growth of vascular and cardiac muscles. AT(1) receptor blockers relax vascular smooth muscle, increase salt excretion, decrease cellular hypertrophy and induce antihypertensive effect without modifying heart rate or cardiac output (3). Most of the AT(1) receptor blockers in use control BP for 24 h with a once-daily dose, without evidence of tolerance to the antihypertensive effect and with a low incidence of side-effects even on long-term use. Monotherapy in mild-to-moderate hypertension controls BP in 40–50% of these patients. The efficacy is similar to angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium antagonists and β-blocking agents (4). AT(1) receptor blockers are specially indicated in patients with hypertension who, being treated with ACE inhibitors, develop side-effects such as cough or angioedema (5). Recent studies have suggested that some AT(1) receptor blockers may act as nephroprotective drugs in diabetes, which is the main cause of renal insufficiency in Western countries (6). Moreover, some AT(1) receptor blockers appear to act as diabetic preventive agents because of its direct effect on pancreatic islets and on improving action insulin resistance (7). However, there is a general lack of comparative data relative to the effect of long-term treatment with different AT(1) receptor blockers on biochemical markers of insulin resistance and metabolic syndrome in diabetic patients. More recently, Schupp et al. (8) demonstrated that telmisartan and irbesartan could be considered as partial and selective peroxisome proliferator-activated receptor (PPAR) γ modulators in their in vitro study.

The aim of our clinical study was to compare the metabolic effect of telmisartan and irbesartan in subjects treated with rosiglitazone, a well-known insulin-sensitizing drug.

**PATIENTS AND METHODS**

**Study design**

This 12-month, multi-centre, double-blind, randomized, controlled trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy), the ‘G. Descovich’ Atherosclerosis Study Center, ‘D. Campanacci’ Clinical Medicine and Applied Biotechnology Department, University of Bologna (Bologna, Italy) and at the Diabetes Care Unit at S. Carlo Hospital of Milan (Milan, Italy).

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments.

**Patients**

Caucasian patients, aged ≥18 years, of either sex were eligible for inclusion in the study if they had type 2 DM according to the American Diabetes Association (ADA) criteria (9) (duration, ≥6 months), and if they had poor glycaemic control [glycosylated haemoglobin (HbA 1c) level, >7.0%] or experienced adverse effects (AEs) with diet and oral hypoglycaemic agents, such as sulphonylureas or meglitinide derivates or acarbose, or metformin, both given up to the maximum tolerated dose. All patients were diagnosed with metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III classification (10). The patients presented with low high density lipoprotein-cholesterol [HDL-C: <40 mg/dL (men) and <50 mg/dL (women)] (10), and hypertension according to the World Health Organization criteria (11) [systolic/diastolic blood pressure (SBP/DBP): ≥130/≥85 mmHg]. All patients had a fasting C-peptide level >1.0 ng/mL. They were overweight [body mass index (BMI): 26.5–28.9 kg/m²] (12). Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had a history of ketoacidosis or unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function [defined as plasma aminotransferase and/or γ-glutamyltransferase level higher than the upper limit of normal (ULN) for age and sex], impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anaemia. Patients with serious cardiovascular disease (e.g. New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of
study enrolment were also excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded. No patients were taking antihypertensive drugs, whereas 49 patients (26.9%) were taking lipid-lowering therapy [seven subjects, rosuvastatin (14.3%); 13 subjects, atorvastatin (26.5%); 15 subjects, simvastatin (30.6%); eight subjects, pravastatin (16.3%); and six subjects, fluvastatin (12.2%)]. All patients provided written informed consent to participate.

**Treatment**

All patients received various treatments (sulphonylureas or meglitinide derivatives or acarbose, or metformin) for type 2 DM, self-administered for 12 months. The doses depended on the tolerance or glycaemic control of the patients with different mean dosages. They were also taking rosiglitazone (4 mg once daily).

In addition, patients were randomized (using envelopes containing randomization codes prepared by a statistician) to receive a dose of 40 mg telmisartan or 150 mg irbesartan, daily once, self-administered for 12 months each day after breakfast. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual patients in cases of emergency, such as hospitalization or suspect of a serious AE.

Telmisartan and irbesartan were supplied as identical, opaque, white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we gave them a bottle containing a 100-day supply of study medication. Throughout the study, we instructed the patients to take their first dose of new medication on the day after they were given the study medication. A bottle containing the study medication for the next treatment period was given to the participants at the 3-month visit. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

**Diet and exercise**

At baseline, patients began a controlled-energy diet (~600 kcal daily deficit), based on ADA recommendations, that contained 50% of calories from carbohydrates, 30% from fat (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fibre. Each centre’s standard diet advice was given by a dietitian and/or specialist physician. Every 2 weeks, dietitians and/or specialists provided instruction on dietary intake, recording procedures as part of a behaviour-modification programme, and then from month 1, they used the patients’ food diaries for counselling. During the study, behaviour-modification sessions on weight-loss strategies were given to individual patients at baseline, one at 6 months, and the other at 12 months. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle 20–30 min, for three to five times per week. The recommended changes in physical activity throughout the study were not assessed.

**Efficacy, tolerability and compliance assessments**

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, measurements of height and body weight, calculation of BMI, assessment of glycaemic control [HbA1c, fasting plasma glucose and insulin levels (FPG and FPI respectively) and Homa-IR, lipid profile (total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), HDL-C and triglycerides (TG)], SBP, DBP, adiponectin and resistin.

Body mass index, HbA1c, FPG, FPI, Homa-IR, lipid profile, SBP, DBP, adiponectin and resistin values were also assessed at 6 and 12 months. Changes in Homa-IR, lipid profile, SBP, DBP, adiponectin and resistin variables were the primary efficacy factors. HbA1c, FPG and FPI were also used to assess efficacy.

All plasmatic variables were determined after a 12-h overnight fast. Venous blood samples were drawn by a research nurse, between 8:00 and 9:00 AM. We used plasma obtained by the addition of Na2-EDTA, 1 mg/mL, and centrifuged at 3000 g for 15 min at 4 °C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for ≤3 months. All measurements were performed in a central laboratory.
Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated using the Homa-IR, with the following formula: Insulin resistance = FPI (μU/mL) × FPG (mmol/L)/22.5, as described by Matthews et al. (13) (normal if <2.5, marker of insulin resistance if ≥2.5). BP measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkometer 3000; ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was measured by the same investigator at each visit in the morning, before daily drug intake and after the patient had rested for ≥10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals, and the mean of the three readings was calculated. BP measurements were performed by physicians not belonging to the immediate study to preserve blinding.

Laboratory technicians drew blood samples, and the biologist responsible for the laboratory performed the assays. HbA1c level was measured using high-performance liquid chromatography (DIAMAT; Bio-Rad Laboratories, Inc., Hercules, CA, USA; normal value, 42–62%), with intra- and inter-assay coefficients of variation (CsV) of <2%. Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) with intra- and inter-assay CsV <2%. Plasma insulin was assayed with Phadiaseph insulin radioimmunoassay (Pharmacia, Uppsala, Sweden) using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and inter-assay CsV, 4.6 and 7.3% respectively).

Total cholesterol and TG levels were determined using fully enzymatic techniques on a clinical chemistry analyser (Hitachi 737; Hitachi, Tokyo, Japan); intra- and inter-assay CsV were 1.0 and 2.1% for TC measurement, and 0.9 and 2.4% for TG measurement respectively. HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid; intra- and inter-assay CsV were 1.0 and 19% respectively. LDL-C level was calculated using the Friedewald formula. Adiponectin level was determined using enzyme-linked immunoassay (ELISA) kits (B-Bridge International, Inc., Sunnyvale, CA, USA). The intra-assay CsV was 36% for low and 33% for high control samples, whereas the inter-assay CsV was 3.2% for low and 7.3% for high control samples (14); resistin value was measured by a commercially available ELISA kit (BioVendor Laboratory Medicine, Inc., Brno, Czech Republic). The intra-assay CsV was 3.4% and the inter-assay CsV was 6.9% (15).

Treatment tolerability was assessed at each study visit using an accurate interview of patients by the investigators, and by comparing the clinical and laboratory values with baseline levels. Medication compliance was assessed by the investigators by counting the number of pills returned at the time of specified clinic visits.

Statistical analysis

An intention-to-treat analysis was conducted in patients who had received ≥1 dose of study medication, and had a subsequent efficacy observation. Patients were included in the tolerability analysis, if they had received ≥1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. The null hypothesis that the expected mean SBP, DBP, Homa-IR, lipid profile, adiponectin and resistin change from baseline to 12 months of double-blind treatment did not differ significantly between telmisartan and irbesartan treatments was tested using analysis of variance and analysis of covariance (ANCOVA) models. Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A one-sample t-test was used to compare values obtained before and after treatment administration; two-sample t-tests were used for between-group comparisons. The Bonferroni correction for multiple comparisons was also carried out. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean (SD). For all statistical analyses, P < 0.05 was considered statistically significant.

RESULTS

Study sample

A total of 188 patients were enrolled in the trial. Of these patients, 182 completed the study and 92
(50.5%) were randomized to double-blind treatment with telmisartan and 90 (49.5%) with irbesartan. There were six patients (three males and three females) who did not complete the study, and the reasons for premature withdrawal included protocol violation, loss to follow-up and non-compliance. The characteristics of the patient population at the initial period of the study, as shown in Table 1, were similar in the two treatment groups. Treatments with oral hypoglycaemic agents were similar and were not significantly different between groups, as well.

**Efficacy**

**Body mass index** No mean BMI change was observed after 6 and 12 months in either group. There was no difference in the mean BMI value of the subjects in the telmisartan and irbesartan groups (Table 1).

**Glycaemic control.** Significant decreases in HbA\textsubscript{1c} and FPG were observed after 6 months ($P < 0.05$) in the telmisartan group and after 12 months in both groups ($P < 0.01$ and $P < 0.05$ respectively). Furthermore, after 12 months, HbA\textsubscript{1c} and FPG decreases were significantly larger ($P < 0.05$) in the telmisartan group than in the irbesartan group (Table 1).

Fasting plasma insulin did not show any significant variation relative to baseline after 6 months, but decreased significantly at 12 months ($P < 0.05$) in both treatment groups; the decrease was significantly larger, after 12 months ($P < 0.05$), in the telmisartan group compared with irbesartan group (Table 1), as well. Significant decreases in Homa-index were obtained at 6 and 12 months ($P < 0.05$ and $P < 0.01$ respectively) in both treatment groups compared with the baseline value. One more time, the Homa-IR lowering was significantly larger in the telmisartan group than the irbesartan group after 12 months ($P < 0.05$; Table 1).

**Blood pressure variables.** Significant SBP and DBP lowering ($P < 0.05$ and $P < 0.01$ respectively) were observed after 6 and 12 months in both the telmisartan and irbesartan groups. There was no significant difference in the antihypertensive effect of the two drugs (Table 1).

**Lipid and lipoprotein variables.** Similar significant decreases in TC and LDL-C ($P < 0.05$ and $P < 0.01$

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<tr>
<th>Table 1. Baseline characteristics and parameter changes at 6 and 12 months of the study in both groups</th>
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<td><strong>Telmisartan + rosiglitazone</strong></td>
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<td><strong>Baseline</strong></td>
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Data are mean values ± SD.
BMI, body mass index; HbA\textsubscript{1c}, glycosylated haemoglobin; FPG, fasting plasma glucose; FPI, fasting plasma insulin; Homa-IR, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides.

*P < 0.05 vs. baseline; **P < 0.01 vs. baseline; ^P < 0.05 vs. irbesartan + rosiglitazone.
respectively) were observed with telmisartan and irbesartan treatments after 6 and 12 months compared with the baseline values (Table 1).

No significant HDL-C and TG changes were observed in either telmisartan or irbesartan groups at either assessment points when compared with the baseline (Table 1).

Adipocytokine measurements. Although at 12 months both treatment groups showed a significant increase in adiponectin concentration ($P < 0.01$ and $P < 0.05$ respectively), at 6 months the change, relative to baseline, was significant only in the telmisartan group. The adiponectin increase was significantly larger in the telmisartan group than in the irbesartan group ($P < 0.05$) (Table 1) (Fig. 1).

Resistin levels decreased significantly, relative to baseline, after 6 months ($P < 0.05$) and 12 months ($P < 0.01$) in the telmisartan group. In the irbesartan group, the change was significant only at 12 months ($P < 0.05$). The decrease in resistin level was significantly larger after 12 months ($P < 0.05$) in the telmisartan group than in the irbesartan group (Fig. 2).

**DISCUSSION**

In patients with type 2 DM, the main aims are to prevent the emergence of insulin resistance, to maintain a favourable lipid profile, and to control hypertension in order to minimize cardiovascular complications and improve patient’s prognosis (16).

Telmisartan has already been demonstrated to have a renoprotective effect, similar to that achieved with enalapril (17), and to have a good metabolic effect in diabetic patients (18). Similar results have been observed also with irbesartan (19, 20). As expected from previous reports (21–23), in this study, both drug regimens also had a significant and persistent antihypertensive effect.

Both drug regimens had a similar positive effect on LDL-C after 6 months of treatment (around 8% reduction), whereas at 12 months, we observed a 22.5% reduction in the telmisartan group vs. 13.3% in the irbesartan group (difference not statistically significant). This result is particularly impressive considering that usually rosiglitazone treatment has the tendency to slightly but significantly increase LDL-C in diabetic patients (24, 25). At 6 months, only the telmisartan-treated patients experienced a significant improvement in glucose homeostasis parameters ($\text{HbA}_1\text{c} = -10.5\%$, FPG = $-9.7\%$, Homa-IR = $-16.7\%$) and in overweight-related parameters (adiponectin = +16.9%, resistin = $-13.3\%$). After 12 months of treatment, both groups experienced an improvement in glucose parameters, significantly larger in the...
Telmisartan-treated group compared with the irbesartan-treated group: HbA1c = −15.8% vs. 10.4%, FPG = −16.0% vs. −6.4%, FPI = 15.3% vs. −8.6% and Homa-IR = 29.2% vs. −17.4% respectively. After 12 months of treatment, adiposity-related parameters improved also in the irbesartan group, but less markedly.

Some AT(1) receptor blockers induce synthesis of adiponectin, an adipose-specific protein adiponectin that has been recently discovered to improve insulin sensitivity, presumably via PPAR γ activation involving a post-transcriptional mechanism (26).

Of course, our study has the limitation of being a relatively small one on well-selected patients. However, the standardization of the antidiabetic treatment with a well-known insulin-sensitizing agent helps to understand the relative contribution of metabolic normalization with the tested antihypertensive agents. In fact, rosiglitazone and other PPAR γ activators are already known to be able to increase adiponectin plasma level (27). In our study, this effect appears to be enhanced more with telmisartan than with irbesartan.

To the best of our knowledge, no direct comparison has been carried out on the effect of telmisartan and irbesartan on such a wide range of metabolic parameters in patients affected by diabetes and metabolic syndrome. Telmisartan or irbesartan act as dissociation/binding selective cofactors that provide the molecular link between ligand-induced conformational changes of PPAR γ and selective gene regulation, and the triggering of specific metabolic in vitro/in vivo effects (28–30). Analysis of PPAR γ protein conformation using protease protection showed that telmisartan and irbesartan interact directly with the receptor, producing a distinct conformational change compared with pioglitazone (8). In fact, telmisartan and irbesartan are characterized as PPAR γ activating agents, called selective PPAR modulators.

In conclusion, our data are consistent with the recent data reported by Schupp et al. (8); telmisartan and irbesartan can be considered as selective PPAR γ activators, which improve insulin sensitivity. The observed differences in metabolic effects of the different AT(1) receptor blockers could be relevant in therapeutic choice for the management of the metabolic syndrome and diabetes.

REFERENCES


