TOP TRIALS REVIEW

Telmisartan: PPAR-γ Activation and Metabolic Effects

Introduction

Evidence from a range of excellent clinical trials proves that lowering BP with several classes of antihypertensive drugs, including angiotensin II type 1 receptor blockers (ARBs), will reduce the complications of hypertension. ARBs, along with other antihypertensives, are beneficial in reducing stroke, coronary vascular disease and nephropathy in patients with diabetes, and have favourable effects on the progression of diabetic and non-diabetic renal disease. Indeed, clinical trial evidence and guidelines provide compelling indications for the use of ARBs in hypertension, particularly when accompanied by diabetes, heart failure or kidney disease. However, there is growing evidence that not all ARBs are the same.

The metabolic syndrome is characterised by the presence of a group of metabolic risk factors including abdominal obesity, insulin resistance, raised BP, and atherogenic dyslipidaemia. People with the metabolic syndrome are at strong risk for the development of diabetes and CVD. The availability of antihypertensives that have a beneficial effect on insulin resistance and dyslipidaemia would have considerable value in clinical practice.

The peroxisome proliferator-activated receptor-γ (PPAR-γ) plays an important role in the regulation of carbohydrate and lipid metabolism. Drugs that activate PPAR-γ are beneficial in improving insulin sensitivity and treating diabetes. There are currently two full PPAR-γ agonists approved to treat diabetes, the thiazolidinediones: rosiglitazone and pioglitazone. However, these agents are associated with a number of limiting side effects such as sodium retention, oedema, weight gain and, in at-risk individuals, the induction of congestive heart failure. Telmisartan has also recently been shown to stimulate PPAR-γ, but because it is a partial agonist, it may not be associated with the same adverse properties of full PPAR-γ agonists. Such findings have major clinical implications, suggesting that ARBs could have unique potential for the prevention and treatment of diabetes and cardiovascular disease in high-risk populations. Large clinical trials will eventually be needed to determine whether clinical doses of ARB agents are able to render significant antimetabolic effects in addition to their antihypertensive effects, given that ARB agonism of PPAR-γ appears to be concentration-dependent. At this early stage, telmisartan appears the most promising in the class because it is associated with more pronounced effects at doses equal to physiologic levels compared with other ARBs. This review accordingly examines the emerging data from preclinical and clinical trials investigating the distinctive metabolic characteristics of telmisartan.

Clinical studies are presented in a summarised form to highlight the most important details of each study. Each summary is evaluated to provide essential information about the objectives, methodology and scientific relevance of the selected study.

Underpinning the clinical trials, evidence from preclinical studies which have revealed the unique metabolic properties of telmisartan are also evaluated and summarised. Finally, sources providing a background, such as review articles, are examined and their observations presented.

We are sure that physicians will benefit from the expert evaluation of our scientists at ADIS INTERNATIONAL MEDICAL EDITIONS and, also, that the Top Trials Review® will provide clinical support for physician's consultations.

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Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR-γ-modulating activity

Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, et al.
Hypertension 2004; 43 (5): 1–10
Preclinical study [English]
California State University, Hayward, California, USA; Bethesda Pharmaceuticals, Inc., Bakersfield, California, USA

Adis evaluation

Study messages

Metabolic Effects: Telmisartan is a partial agonist of PPAR-γ and reduces glucose, insulin and triglyceride levels in rats fed a high-fat, high-carbohydrate diet.
Clinical relevance: A

Study objective

This study investigated the effects of telmisartan and other angiotensin II type 1 receptor blockers (ARBs) on peroxisome proliferator-activated receptor-γ (PPAR-γ) activity in murine cells. The comparative effects of telmisartan and losartan on glucose, insulin and triglyceride levels in rats fed a high-fat, high-carbohydrate diet were also assessed.

Study details

Design: *in vivo, in vitro*
Control: drug comparison, untreated control group comparison
Phase: preclinical
Location: USA
Criteria for evaluation: PPAR-γ activity, body weight, glucose levels, insulin levels, triglyceride levels.
Methods: *In vitro* studies – PPAR-γ was determined by transactivation assays in CV-1 cells following treatment with varying concentrations of telmisartan, irbesartan, candesartan cilexetil, valsartan, olmesartan medoxomil, eprosartan and losartan.
In vivo studies – 6-week-old male Sprague-Dawley rats were fed on a high-fat, high-carbohydrate diet. Two days after starting the diet the rats were randomised to receive telmisartan, losartan (dosage of both drugs at ~5 mg/kg/day) or no treatment for 14 weeks. Serum glucose, insulin and triglycerides were assessed after 5 weeks. The protocol was continued for an additional 9 weeks at which time an oral glucose tolerance test was performed.

Subjects

Type: animals

Treatments

Drugs: telmisartan, losartan

Results

Telmisartan was the only ARB that caused substantial activation of PPAR-γ. Telmisartan functioned as a moderately potent, selective PPAR-γ partial agonist, activating the receptor to 25–30% of the maximum level achieved by the full agonists rosiglitazone and pioglitazone. Telmisartan also increased the expression of known PPAR-γ target genes and induced adipogenesis in pre-adipocyte fibroblasts.
Administration of telmisartan to rats caused a significant attenuation of weight gain compared with

losartan and controls (~10%). This could not be attributed to reduced energy intake as food intake was nearly identical in all treatment groups. Serum glucose levels significantly decreased after 5 weeks of treatment with telmisartan compared with both losartan ($p < 0.01$) and controls ($p < 0.001$). Serum insulin levels also tended to be lower in telmisartan-treated rats ($0.05 < p < 0.10$). Serum triglycerides were significantly decreased in the telmisartan treated group compared with both the losartan group ($p < 0.05$) and controls ($p < 0.01$).

During the oral glucose tolerance test, serum glucose levels were similar between all three treatment groups. However, serum insulin levels were significantly lower in the telmisartan group compared with the losartan and control groups.

Losartan did not have any significant effects on any of the parameters measured when compared with controls.

Conclusions

"Aside from the potential use of telmisartan for the prevention and treatment of diabetes and the metabolic syndrome, the discovery that telmisartan can activate PPAR-γ has a number of implications for the development of next-generation molecules for treating clinical disorders that are influenced by activity of the renin-angiotensin system and PPAR-γ. …ARBs that ameliorate insulin resistance and dyslipidemia as well as hypertension could provide even more effective options for preventing target-organ damage and cardiovascular disease in patients with hypertension, diabetes, or both. Such agents, either alone or in combination with ACE inhibitors, could also be useful for the prevention of new-onset diabetes in patients with hypertension or in other high-risk populations."

Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-γ activity

Schupp M, Janke J, Clasen R, Unger T, Kintscher U
Circulation 2004; 109 (17): 2054–2057
Preclinical study [English]
Charité-Universitätsmedizin Berlin, Berlin, Germany

Adis evaluation

Study messages

Metabolic Effects: Telmisartan, at physiological doses, and irbesartan at higher doses induce PPAR-γ activity, thereby promoting PPAR-γ-dependent differentiation in 3T3-L1 adipocytes, independent of AT_1 receptor blockade.

Clinical relevance: A

Study objective

Angiotensin type 1 (AT_1) receptor antagonism has been shown to lower the risk for type 2 diabetes compared with other antihypertensive therapies. In addition, AT_1 receptor blockade improved insulin sensitivity in animal models of insulin resistance.

This study investigated the effects of telmisartan and other angiotensin II type 1 receptor blockers (ARBs) on peroxisome proliferator-activated receptor-γ (PPAR-γ) function in 3T3-L1 cells to clarify the underlying mechanisms of the antidiabetic effects of ARBs.

Study details

Design: *in vitro*
Control: drug comparison
Phase: preclinical
Location: Germany
Criteria for evaluation: PPAR-γ activity
Methods: Cultured mouse 3T3-L1 pre-adipocyte cells were treated with vehicle or the ARB ± pioglitazone until day 4 of differentiation. The effects of ARBs on lipid accumulation and adipocyte differentiation were investigated using real-time polymerase chain reaction (PCR), and effects on PPAR-γ activity were investigated using transcription reporter assays. The PPAR-γ ligand pioglitazone was used as a control.

Treatments

Drugs: telmisartan, eprosartan, irbesartan, losartan

Results

Telmisartan and irbesartan potently enhanced lipid accumulation, and increased PPAR-γ-dependent 3T3-L1 adipocyte differentiation, as shown by a significant increase in mRNA expression of the adipogenic marker gene adipose protein 2 (aP2) (irbesartan 10 μmol/L, 3.3-fold induction; telmisartan 10 μmol/L, 3.1-fold induction; both $p < 0.01$). There was a more pronounced induction of aP2 expression at lower, pharmacologically relevant concentrations with telmisartan, compared with the other ARBs. In contrast, losartan enhanced aP2 expression only at high concentrations (losartan 100 μmol/L: 3.6-fold induction; $p < 0.01$). Eprosartan at concentrations ≤ 100 μmol/L had no significant effects.

Irbesartan and telmisartan (10 μmol/L) markedly induced PPAR-γ transcriptional activity, by 3.4-fold and 2.6-fold ($p < 0.05$), respectively, compared with 5.2-fold stimulation by the PPAR-γ ligand pioglitazone 10 μmol/L.

Irbesartan and telmisartan also induced PPAR-γ activity in an AT_1 receptor-deficient cell model (PC12W), demonstrating that these ARBs stimulate PPAR-γ activity independent of AT_1 receptor-blocking activity.

Conclusions

"Telmisartan, the ARB with the highest lipophilicity, most potently induced PPAR-γ-dependent aP2 expression and PPAR-γ2 LBD [ligand-binding domain] activation at pharmacologically relevant concentrations. These data imply that PPAR-γ activating potency correlates with the degree of lipophilicity among the ARBs (telmisartan > irbesartan > losartan)…"

"PPAR-γ activation by a specific subset of ARBs may provide new therapeutic options in the treatment of patients with the metabolic syndrome. In addition, the pharmacological characteristics of PPAR-γ-activating ARBs may serve as a starting point for the development of future substances combining dual functions (AT_1R [receptor] antagonism and PPAR-γ activation) to treat hypertension and insulin resistance/type 2 diabetes."

An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes

Fujimoto M, Masuzaki H, Tanaka T, Yasue S, et al.
FEBS Letters 2004; 576 (3): 492–497
Preclinical study [English]
Kyoto University Graduate School of Medicine, Kyoto, Japan

Adis evaluation

Study messages

Metabolic effects: Telmisartan augments GLUT4 protein expression and 2-deoxy glucose uptake in basal and insulin-stimulated adipocytes.

Clinical relevance: B

Study objective

Clinical trials have shown that some angiotensin II type 1 receptor blockers (ARBs) have insulin sensitising properties. Furthermore, the ARB telmisartan has been shown to share a structural similarity with pioglitazone, and can serve as a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ). However, the underlying mechanism associated with the insulin-sensitising effects of telmisartan are unclear.

This study investigated the effect of telmisartan on insulin action in 3T3-L1 adipocytes.

Study details

Design: *in vitro*

Control: drug comparison

Phase: preclinical

Location: Japan

Criteria for evaluation: GLUT4 expression, glucose uptake

Methods: Cultured 3T3-L1 pre-adipocytes were differentiated in the presence of varying concentrations of telmisartan, valsartan and pioglitazone to investigate effect on adipogenesis. To elucidate regulation of PPAR-γ downstream genes in differentiating and mature adipocytes, the compounds were added to the differentiation media on day 2 or day 8, followed by Northern blot analyses of adipose protein 2 (aP2) and adiponectin mRNA. Impact on glucose transportation was examined by 2-deoxy glucose uptake assays, and impact on GLUT4 protein expression was assessed by Western blot analyses. The PPAR-γ agonist pioglitazone was used as a control.

Treatments

Drugs: telmisartan, valsartan

Results

Higher concentrations (1 and 10 μmol/L), but not 0.1 μmol/L, of telmisartan facilitated differentiation of 3T3-L1 cells. However, valsartan had no effect on adipogenesis, even at a concentration of 10 μmol/L. As expected, pioglitazone 1 μmol/L facilitated pre-adipocyte differentiation.

Treatment of both differentiating adipocytes and fully differentiated adipocytes with telmisartan 10 μmol/L caused an increase in mRNA levels for PPAR-γ target genes such as aP2 and adiponectin. Valsartan did not augment expression of PPAR-γ target genes in either differentiating or mature adipocytes. Gene expression of 11γ-HSD1 was not changed by the compounds during differentiation of 3T3-L1 cells, but was significantly decreased by telmisartan 10 μmol/L, but not valsartan, in differentiated adipocytes.

Telmisartan 1 or 10 μmol/L significantly increased glucose uptake in differentiated 3T3-L1 adipocytes in the presence or absence of insulin. Valsartan did not affect glucose uptake. Furthermore, Western blot analyses showed that GLUT4 protein expression was significantly enhanced (compared with vehicle) when cells were differentiated with telmisartan 1 or 10 μmol/L. Valsartan did not augment GLUT4 protein expression.

Conclusions

"The present study first provides evidence that telmisartan enhances glucose uptake in cultured adipocytes, accompanied by an increase in GLUT4 expression. Coordinated regulation of mRNA expressions for adiponectin and 11γ-HSD1 in adipocytes may also be beneficial for insulin-sensitizing effects by telmisartan. Our data provide a fresh insight into improved therapeutic approaches to treat type 2 diabetes, hypertension with insulin resistance and the metabolic syndrome."

Partly funded by the Takeda Medical Research Foundation.

Telmisartan is a dual ARB and PPAR gamma activator that limits weight gain, body fat accumulation, and adipocyte size in rats fed high fat, high carbohydrate diets

Qi N, Pravenec M, Ho CI, Benson SC, Pershadsingh HA, et al.
Presented at the 58th Annual Fall Conference and Scientific Session of the Council for High Blood Pressure Research in Association with the Council on the Kidney in Cardiovascular Disease held in Chicago, Illinois, USA in October 2004.
Preclinical study [English]
University of California, San Francisco, California, USA

Adis evaluation

Study messages

Metabolic effects: Telmisartan therapy is associated with significantly lower accumulation of subcutaneous and epididymal fat compared with controls in rats fed a high-fat, high-carbohydrate diet.

Clinical relevance: **B**

Study objective

Preclinical studies have suggested that the acetyl-CoA carboxylase 2 (ACC2) gene plays an essential role in controlling fatty acid oxidation. ACC2-deficient mice fed a high-fat, high-carbohydrate diet have a higher fatty acid oxidation rate, accumulate less fat and live a normal lifespan compared to wild-type mice which develop diabetes when given the same diet. It is hypothesized that telmisartan may suppress the ACC2 gene and that this may explain its effects on weight gain. This study investigated the mechanism by which telmisartan attenuates weight gain in rats fed a high-fat, high-carbohydrate diet.

Study details

Design: *in vivo*
Control: untreated control group comparison
Phase: preclinical
Location: USA
Criteria for evaluation: body weight, adipose tissue mass, adipocyte size
Methods: Rats were treated with and without telmisartan 5 mg/day orally once daily for 5 months

Subjects

Type: animals

Treatments

Drugs: telmisartan

Results

Outcomes at 5 months	Telmisartan	Controls	P value
Body weight (g)	435.4	509.6	0.05
Food intake (g/100g of body weight/day)	3.80	3.69	--
Subcutaneous fat (g/100g of body weight)	1.14	1.49	0.05
Epididymal fat (g/100g of body weight)	1.59	1.84	0.05
Adipocyte diameter (microns)	80.5	96.9	0.05

Conclusions

"The current findings suggest that telmisartan attenuates diet induced weight gain by limiting fat accumulation, possibly by increasing fatty acid oxidation through suppression of ACC2."

Insulin-sensitizing effects of telmisartan: Implications for treating insulin-resistant hypertension and cardiovascular disease

Pershadsingh HA, Kurtz TW
Diabetes Care 2004; 27 (4): 1015
Case report [English]
Kern Medical Center, Bakersfield, California, USA

Adis evaluation

Study messages

Metabolic effects: Telmisartan may improve insulin resistance and lower triglycerides in obese hypertensive patients with impaired glucose tolerance. Switching to valsartan appears to reverse these improvements.

Clinical relevance: C

Study objective

This case report described the effects of telmisartan on lipid parameters, glucose and insulin levels in an obese hypertensive patient with impaired glucose tolerance. The effect of switching to valsartan was also reported.

Study details

Design: Case report

Location: USA

Criteria for evaluation: plasma glucose, plasma insulin, homeostasis model of insulin resistance (HOMA-IR), body weight, total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol

Subjects

Type: patients

Number: 1

Gender: male

Age: 52 years

Patient characteristics: the patient had visceral obesity (body mass index 34.4 kg/m^2) and impaired glucose tolerance.

Indication: hypertension

Treatments

Drug	Telmisartan	Valsartan	Telmisartan
Dose	80 mg/day	160 mg/day	80 mg/day
Route	PO	PO	PO
Duration	Weeks 1–10	Weeks 11–15	Weeks 16–19
Status	Launched	Launched	Launched

Results

	Baseline	Telmisartan Week 10	Valsartan Week 15	Telmisartan Week 19
Fasting blood glucose (mmol/L)	6.83	5.78	6.12	5.94
Fasting insulin (µU/mL)	30	15	22	19
HOMA-IR	9.11	3.85	5.98	5.02
Fasting triglycerides (mmol/L)	1.54	1.21	1.57	1.40

As shown in the table, the patient's insulin resistance and triglyceride levels improved on telmisartan, but deteriorated when switched to valsartan, an angiotensin II type 1 receptor blocker that does not activate peroxisome proliferator-activated receptor-γ (PPAR-γ).

Body weight, total cholesterol, HDL cholesterol and LDL cholesterol remained unchanged throughout the observation period.

Conclusions

"These findings may provide a new basis for drug choice in insulin resistance and hypertension and should motivate systematic studies on the therapeutic effects of telmisartan in patients with insulin resistance and related metabolic and cardiovascular diseases. ARBs [angiotensin II receptor blockers] that activate PPAR-γ might exert beneficial effects on carbohydrate and lipid metabolism that could promote improved cardiovascular outcomes."

Safety of telmisartan in patients with arterial hypertension: an open-label observational study

Michel MC, Bohner H, Köster J, Schäfers R, Heemann U
Drug Safety 2004; 27 (5): 335–344
Clinical study [English]
University of Amsterdam, Amsterdam, The Netherlands; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Adis evaluation

Study messages

Efficacy: Telmisartan is effective in improving BP in patients with essential hypertension, regardless of age, sex, concomitant disease and/or previous or present use of antihypertensive medication.
Tolerability: Telmisartan is well tolerated in patients with essential hypertension, regardless of age, sex, concomitant disease and/or previous or present use of antihypertensive medication.
Metabolic effects: Telmisartan reduces serum glucose, triglyceride and cholesterol levels in patients with a range of comorbidities (diabetes, hypercholesterolaemia, coronary heart disease, congestive heart failure, renal insufficiency). The reductions are most pronounced in patients with diabetes and hypercholesterolaemia.
Adis score: 58
Positive features: clear study aim; large number of patients in each treatment group; study duration sufficient to fulfil aim; details of concomitant medication included; results and adverse events well reported; good discussion and review of others' work
Negative features: open non-randomised trial; compliance not reported; methods reported briefly
Clinical relevance: B

Study objective

The efficacy and tolerability of antihypertensive therapies can be affected by patient age, gender, concomitant morbidity and/or concurrent medication. Controlled clinical studies performed in specific patient populations may exclude such factors. Therefore, large-scale evaluations under real-life conditions may better reflect safety and efficacy encountered in day-to-day clinical practice.
This observational post-marketing surveillance study examined the effects of age, gender, concomitant disease and/or previous antihypertensive treatment on the tolerability and efficacy of telmisartan in patients with essential hypertension.

Study details

Design: multicentre, post-marketing surveillance
Control: baseline comparison, patient comparison
Phase: IV
Location: Germany
Criteria for evaluation: clinical response rate, diastolic blood pressure, systolic blood pressure
Methods: Physicians in Germany systematically documented observations for five consecutive hypertensive patients scheduled to receive telmisartan based on the physician's medical judgement. No specific inclusion or exclusion criteria were specified, other than a minimum age of 18 years. Patients were to receive telmisartan as monotherapy or as part of antihypertensive combination therapy. Measurement of serum creatinine, potassium, glucose, triglycerides and/or total cholesterol was optional.

Subjects

Type: patients
Number: 19,870
Gender: male & female
Age: 18–99 years
Patient characteristics: Patients had essential hypertension. Concomitant diseases included: diabetes mellitus (18% of patients), hypercholesterolaemia (48%), coronary heart disease (20%), congestive heart failure (13%), renal insufficiency (2%), gastrointestinal complaints (11%), rheumatic disorders (10%) and obstructive airway disease (8%). Thirty-two percent of patients received telmisartan monotherapy without having had any previous antihypertensive therapies, 33% of patients replaced existing therapies with telmisartan monotherapy and the remainder used telmisartan in addition to previous medication. Baseline BP was slightly lower in patient groups receiving telmisartan as replacement or in addition to previous antihypertensive medications when compared to patients receiving it for first time treatment.
Indication: essential hypertension

Treatments

Drug	Telmisartan
Dose	40 or 80 mg
Route	PO
Frequency	od
Duration	6 months
Status	Launched

Concomitant medication: digoxin, organic nitrates, aspirin, oral antihyperglycaemics, nonsteroidal anti-inflammatory drugs, β2-adrenoceptor agonists, diuretics, β-adrenoceptor antagonists [beta blockers], calcium channel antagonists, ACE inhibitors

Results

	Mean change from baseline after 6 months' telmisartan therapy			
	Blood pressure (mm Hg)	Glucose (mg/dL)	Triglycerides (mg/dL)	Cholesterol (mg/dL)
All patients	–29.7/–15.5	–4.0	–17.4	–16.4
Comorbidity status:				
no comorbidity	–29.9/–16.1	–0.6	–9.1	–0.51
diabetes	–29.8/–14.5	–13.0	–22.7	–17.4
hypercholesterolemia	–29.8/–15.4	–4.9	–22.7	–23.8
coronary heart disease	–29.5/–14.1	–5.5	–17.6	–17.2
congestive heart failure	–28.8/–13.9	–5.7	–17.2	–15.5
renal insufficiency	–29.1/–15.5	–9.1	–12.4	–18.6

Seventy-six percent of patients achieved a full response to treatment (diastolic BP ≤ 90mm Hg or ≥ 10mm Hg reduction) and 22% had an inadequate response to telmisartan therapy (diastolic BP > 90mm Hg or < 7mm Hg reduction). Overall, heart rate was reduced from 78.0 to 73.8 beats/min after 6 months of treatment. The dosage was increased in 24% of patients because of insufficient BP reduction with the lower dosage.

Adverse events

Side effects (% patients)	Telmisartan
Total of patients experiencing adverse events	1.9
Headache	0.3
Dizziness	0.2
Gastrointestinal events	0.4
Back pain	0.1
Bronchitis	0.1
Tachycardia	0.1
Fatigue	0.1
Coughing	0.1
Sleep disorders	0.1

Global tolerability was rated as very good, good, moderate or poor in 75%, 22%, 1% and 1% of patients, respectively. There were no significant differences in global tolerability ratings between the patient groups. Telmisartan had only a minor or no effect on serum creatine levels across all patient groups.

Serious adverse events were reported in 0.06% of patients and included death in 6 patients. None of the deaths were considered drug-related.

Conclusions

"Some classes of antihypertensive drugs… can have adverse effects on the metabolic profile… The present analysis confirms the absence of adverse metabolic effects with telmisartan. Moreover, our data establish that this beneficial profile is maintained across all patient subgroups, including those with diabetes and hypercholesterolemia."

"The present data clearly demonstrate that the excellent tolerability of telmisartan is independent of age, gender and a variety of comorbidities. Moreover, the magnitude of its blood-pressure lowering effect is also largely independent of these factors, as well as of previous or present antihypertensive therapy."

This study was funded by Boehringer Ingelheim.

Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study

Derosa G, Ragonesi PD, Mugellini A, Ciccarelli L and Fogari R
Hypertension Research 2004; 27 (7): 457–464
Clinical study [English]
University of Pavia, Pavia, Italy

Adis evaluation

Treatment outcome

Efficacy: telmisartan ≥ eprosartan > placebo
Tolerability: telmisartan = eprosartan = placebo
Metabolic effects: telmisartan > eprosartan

Study messages

Efficacy: Telmisartan and eprosartan similarly reduce systolic BP but telmisartan produces greater reductions in diastolic BP than eprosartan in hypertensive patients with type 2 diabetes mellitus.
Metabolic effects: Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride levels were improved to a significantly greater extent in telmisartan than eprosartan-treated hypertensive patients with diabetes mellitus ($p < 0.01$). Neither treatment negatively affected body mass index or glucose metabolism.
Tolerability: Both telmisartan and eprosartan were well tolerated in hypertensive patients with type 2 diabetes mellitus. Adverse events were mild in severity and no serious adverse events were reported. No patients withdrew from the study due to adverse events.

Adis score: 80

Positive features: clear study aim; appropriate patient selection and exclusion criteria; adequate number of patients randomised to comparable treatment groups; appropriate dosage and administration of study drugs; study duration sufficient to assess drug efficacy and tolerability; placebo comparison used to control variation; methods and results well reported; adverse events adequately reported; discussion included review of own and others' work

Negative features: limited details of concomitant medication; compliance not reported; study limitations not discussed

Clinical relevance: B

Study objective

The incidence of hypertension in diabetic patients is 1.5–3 times higher than age-matched subjects without diabetes mellitus.
This study compared the efficacy and tolerability of telmisartan with that of eprosartan in hypertensive patients with type 2 diabetes mellitus previously treated only with diet and exercise.

Study details

Design: randomised, double-blind

Control: baseline comparison, drug comparison, placebo comparison

Phase: III

Location: Italy

Criteria for evaluation: body mass index, diastolic blood pressure, systolic blood pressure, fasting glucose level, high-density lipoprotein cholesterol level, proportion of glycosylated haemoglobin, total cholesterol level, triglyceride levels

Methods: There was a 4-week placebo-controlled wash-out period prior to randomisation. Patients who had received prior antihypertensive therapy were taken off their medication for ≥ 4 weeks. Patients were advised to have a dietary intake of 1400–1600 kcal/day and exercise for ≥ 30 minutes on 4 days of the week.

Subjects

Type: patients
Number: 119
Gender: male & female
Age: mean 54 years
Patient characteristics: Patients had type 2 diabetes mellitus of mean duration of 5 years and mild hypertension defined by the World Health Organization-International Society of Hypertension criteria (diastolic BP 90–99mm Hg). Patients had a mean BP of 143/92mm Hg, total cholesterol level of 195 mg/dL, low density lipoprotein (LDL) cholesterol level of 128 mg/dL, high density lipoprotein (HDL) cholesterol level of 42 mg/dL and triglyceride level of 127 mg/dL. They had adequate glycaemic control (proportion of glycosylated haemoglobin < 7.0%).
Indication: essential hypertension, type 2 diabetes mellitus

Treatments

Drug	Telmisartan	Eprosartan
Dose	40 mg/day	600 mg/day
Route	PO	PO
Frequency	od	od
Duration	12 months	12 months
Status	Launched	Launched

Treatment was administered in the morning after breakfast.
Concomitant medication: *not stated*

Results

End of treatment trough diastolic BP was significantly lower with telmisartan compared with eprosartan ($p < 0.05$).
Systolic BP was significantly reduced from baseline after 6 months of treatment with telmisartan or eprosartan ($p < 0.05$). In addition, systolic BP after 6 months was significantly lower in both groups compared with placebo ($p < 0.05$).
Total cholesterol, triglycerides and LDL cholesterol were significantly reduced from baseline after 6 months treatment with telmisartan ($p < 0.05$).
There were no significant changes in body mass index, proportion of glycosylated haemoglobin, fasting plasma glucose, fasting plasma insulin or insulin sensitivity compared with baseline in any of the treatment groups at 6 or 12 months, and no significant differences in values between treatment groups.

	Placebo (n = 40)	Telmisartan (n = 40)	Eprosartan (n = 39)
Systolic BP (mm Hg):			
Baseline	143	143	144
12 months	141	135[ab]	137[ab]
Diastolic BP (mm Hg):			
Baseline	92	92	91
12 months	90	84[ab]	87[cd]
Total cholesterol (mg/dL):			
Baseline	197	195	193
12 months	195	180[ade]	190[a]
LDL cholesterol (mg/dL):			
Baseline	129	130	125
12 months	127	119[ade]	124
HDL cholesterol (mg/dL):			
Baseline	43	42	42
12·months	42	43[ade]	41
Triglycerides (mg/dL):			
Baseline	126	125	129
12 months	128	94[cde]	121

a $p < 0.01$ vs baseline; b $p < 0.01$ vs placebo; c $p < 0.05$ vs baseline; d $p < 0.05$ vs placebo; e $p < 0.05$ vs eprosartan.

Adverse events

Side effects (patients)	Placebo	Telmisartan	Eprosartan
Fatigue	1	1	
Dizziness			2
Headache	1		

Adverse events were mild in severity and no serious adverse events were reported. No patients withdrew from the study due to adverse events.

Conclusions

"These results suggest that there are differences between ARBs [angiotensin-II receptor blockers]. Telmisartan, after administration for 12 months, conferred significant advantages compared with eprosartan in terms of blood pressure control and plasma lipid levels in diabetic patients with hypertension."

Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study

Derosa G, Cicero AFG, Bertone G, Piccinni MN, Fogari E, et al.
Clinical Therapeutics 2004; 26 (8): 1228–1236
Clinical study [English]
University of Pavia, Pavia, Italy

Adis evaluation

Treatment outcome

Efficacy: telmisartan = nifedipine
Metabolic effects: telmisartan > nifedipine
Tolerability: telmisartan > nifedipine

Study messages

Efficacy: Both telmisartan and nifedipine reduce BP in patients with mild hypertension and type 2 diabetes.
Metabolic effects: Telmisartan improves the lipid profile to a greater extent than nifedipine in patients with mild hypertension and type 2 diabetes mellitus, while neither drug has any significant effect on glucose metabolism.
Tolerability: Both telmisartan and nifedipine are generally well tolerated in patients with mild hypertension and type 2 diabetes mellitus.

Adis score: 84

Positive features: clear study aim; appropriate patient selection and exclusion criteria; randomised treatment allocations; appropriate dosage and administration of study drugs; study duration sufficient to assess drug efficacy and tolerability; double-blind trial design; drug comparison used to control variation; compliance assessed using tablet counts; methods, results and adverse events well reported; author discussion included review of own and others' work

Negative features: study limitations not fully discussed

Adis score: 84

Clinical relevance: B

Study objective

Telmisartan is an angiotensin II receptor antagonist highly selective for the angiotensin II type 1 receptor. Nifedipine is a calcium channel antagonist that is known to decrease cardiovascular risk in diabetic patients.

This study compared the efficacy and tolerability of telmisartan and nifedipine gastrointestinal therapeutic system (GITS) in hypertensive patients with type 2 diabetes mellitus. Effects on glucose metabolism and lipid levels were also assessed.

Study details

Design: randomised, double-blind
Control: baseline comparison, drug comparison
Phase: III
Location: Italy
Criteria for evaluation: diastolic BP, systolic BP, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, proportion of glycosylated haemoglobin (HbA_{1c}), body mass index, fasting glucose level, insulin sensitivity
Methods: There was a 4-week washout period prior to randomisation. Patients were advised to have a dietary intake of 1400–1600 kcal/day and exercise for ≥ 30 min four times a week.

Subjects

Type: patients
Number: 116
Gender: male & female
Age: mean 53 years
Patient characteristics: Patients had type 2 diabetes mellitus for a duration of ≥ 2 years with good glycaemic control (HbA_{1c} < 7.0%). Patients had mild hypertension defined by the World Health Organization-International Society of Hypertension criteria (diastolic BP 90–99mm Hg). They had a mean HbA_{1c} of 6.15% and a mean BP of 140/95mm Hg. Antihyperglycaemic and antihyperlipidaemic treatments had been stable for ≥ 2 months. Patients had previous exposure to atenolol (n = 12), metoprolol (10), doxazosin (27), and hydrochlorothiazide (26).
Indication: hypertension

Treatments

Drug	Telmisartan	Nifedipine
Dose	40 mg/day	20 mg/day
Route	PO	PO
Frequency	od	od
Duration	12 months	12 months
Status	Launched	Launched

Concomitant medication: glibenclamide [gyburide] (n = 12), gliclazide (10), glimepiride (17), metformin (34), acarbose (19), repaglinide (24), atorvastatin (31), pravastatin (32), simvastatin (31), fluvastatin (22)

Results

	Telmisartan (n = 58)		Nifedipine (n = 58)	
	Baseline	12 months	Baseline	12 months
Systolic BP (mm Hg)	139	132[a]	140	130[a]
Diastolic BP (mm Hg)	95	86[a]	94	84[a]
Body mass index (kg/m^2)	26.6	26.1	26.9	26.3
HbA_{1c} (%)	6.2	6.3	6.1	6.2
Fasting plasma glucose (mg/dL)	125	121	128	123
Fasting plasma insulin (µU/mL)	18.3	17.1	18.7	18.4
HOMA-IR	4.9	4.7	4.8	4.6
Total cholesterol (mg/dL)	210	191[ab]	207	203
LDL cholesterol (mg/dL)	139	123[ab]	134	132
HDL cholesterol (mg/dL)	43	41	42	40
Triglycerides (mg/dL)	141	132	154	144

HOMA-IR = homeostasis model assessment of insulin resistance.
a $p < 0.01$ vs baseline; b $p < 0.05$ vs nifedipine.

Adverse events

Side effects (patients)	Telmisartan (n = 58)	Nifedipine (n = 58)
Fatigue	1	2
Dizziness	1	1
Headache	0	3

All reported adverse events were mild in severity. No severe or serious adverse events or withdrawals due to adverse events occurred in either treatment group. There were no significant changes in laboratory parameters.

Conclusions

"In this selected sample of patients with type 2 diabetes and mild hypertension, 12 months of treatment with telmisartan conferred a slight but statistically significant advantage in terms of plasma lipid control compared with nifedipine GITS."

Comparative effect of telmisartan and losartan on glucose metabolism in hypertensive patients with the metabolic syndrome

Rosano GM, Vitale C, Castiglioni C, Cornoldi A, Fini M
Circulation 2004; 110 (Suppl.) No. 17: 606 (abstr. 2818)
Clinical study [English]
Presented as a poster in the 77th Scientific Sessions of the American Heart Association (AHA) held in New Orleans, Louisiana, USA in November 2004
San Raffaele Hospital, Rome, Italy

Adis evaluation

Treatment outcome

Efficacy on BP reduction: telmisartan > losartan
Tolerability: telmisartan = losartan
Metabolic effects: telmisartan > losartan

Study messages

Efficacy: Telmisartan improves glycaemic control and reduces BP to a greater extent than losartan in hypertensive patients with metabolic syndrome.
Tolerability: Telmisartan and losartan are well tolerated in hypertensive patients with metabolic syndrome.
Clinical relevance: B

Study objective

Angiotensin II type 1 receptor blockers (ARBs) have been shown to reduce renal and cardiovascular complications in hypertensive patients with diabetes, and to delay the onset of diabetes in non-diabetic patients with hypertension. The ARB telmisartan may have a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonistic effect and may improve glucose tolerance.
This study compared the effects of telmisartan and losartan on BP and glycaemic control in hypertensive patients with metabolic syndrome.

Study details

Design: randomised, double-blind, parallel
Control: baseline comparison, drug comparison
Phase: II
Location: Italy
Criteria for evaluation: BP, 2h plasma glucose level, fasting glucose level, insulin level, insulin resistance, proportion of glycosylated haemoglobin (HbA_{1c})

Subjects

Type: patients
Number: 40
Gender: male & female
Age: 18–75 (mean 56) years
Patient characteristics: Patients had hypertension with a mean 24h ambulatory BP of ≥ 135/85 (mean 143/89) mm Hg, and metabolic syndrome according to the WHO criteria. They had a mean body mass index of 33.5 kg/m^2. Thirty-six patients had impaired glucose tolerance and four had type 2 diabetes mellitus.
Indication: hypertension

Treatments

Drug	Telmisartan	Losartan
Dose	80 mg/day	50 mg/day
Route	PO	PO
Frequency	od	od
Duration	3 months	3 months
Status	Launched	Launched

Results

Change from baseline at 3 months	Telmisartan (n = 20)	Losartan (n = 20)
Ambulatory BP (mm Hg)	–13.7[a]/–8.8[a]	–10.2/–4.8
Fasting plasma glucose (%)	–6.8[b]	+3.0
Fasting plasma insulin (%)	–3.2[b]	+2.9
HOMA-IR (%)	–5.2[b]	+0.9
2h glucose levels after OGTT (%)	–9.4[b]	+2.3
2h insulin levels after OGTT (%)	–8.6[b]	+3.5

HOMA-IR = homeostasis model assessment of insulin resistance; OGTT = oral glucose tolerance test. a $p < 0.05$ vs losartan; b $p < 0.01$ vs losartan.

HbA_{1c} was reduced to a significantly greater extent in patients receiving telmisartan compared with losartan ($p < 0.05$). There was no correlation between decrease in BP and change in fasting plasma glucose ($r = 28$) or fasting plasma insulin ($r = 0.36$).

Adverse events

Both telmisartan and losartan were well tolerated and there were no adverse events reported.

Conclusions

"Telmisartan, unlike losartan, improves glucose metabolism in patients with metabolic syndrome and hypertension. Telmisartan administration for 3 months improves fasting FPG [fasting plasma glucose], post-prandial FPG, insulin sensitivity and HbA_{1c}. The insulin-sensitizing actions of telmisartan may be due to its partial PPAR-γ·agonism. Telmisartan produces significantly greater 24-h mean ambulatory blood pressure reductions than losartan. Telmisartan, therefore, offers a useful treatment option for patients with hypertension and glucose intolerance."

Possible beneficial effect of telmisartan on glycemic control in diabetic subjects

Honjo S, Nichi Y, Wada Y, Hamamoto Y, Koshiyama H
Diabetes Care 2005; 28 (2): 498
Clinical study [English]
Kitano Hospital, Osaka, Japan

Adis evaluation

Study messages

Metabolic effects: Telmisartan may improve glycaemic control compared with candesartan cilexetil in hypertensive Japanese patients with type 2 diabetes mellitus.

Clinical relevance: B

Study objective

This study investigated the effects of telmisartan and candesartan cilexetil on glycaemic control in Japanese patients with type 2 diabetes mellitus and hypertension.

Study details

Design: prospective
Control: drug comparison, drug dosage comparison
Phase: II
Location: Japan
Criteria for evaluation: proportion of glycosolated haemoglobin (HbA_{1c})

Subjects

Type: patients
Number: 38
Gender: male & female
Age: mean 67 years
Patient characteristics: Patients had a mean baseline HbA_{1c} of 7.40–8.12%.
Indication: hypertension

Treatments

Drug	Telmisartan	Candesartan cilexetil
Dose	20 or 40 mg/day	8 mg/day
Route	PO	PO
Duration	3 months	3 months
Status	Launched	Launched

Results

HbA_{1c} (%)	Telmisartan 20 mg/day (n = 9)	Telmisartan 40 mg/day (n = 11)	Candesartan cilexetil 8 mg/day (n = 18)
Decrease from baseline in HbA_{1c} at 3 months	0.04	0.69[a]	0.08

a $p < 0.05$ vs baseline

Conclusions

„This preliminary result is in line with the hypothesis that telmisartan has an insulin-sensitizing effect through PPARγ [peroxisome proliferator-activated receptor-γ] activation. ...A randomized control study with a larger number of subjects may be justified to test whether telmisartan may improve glycemic control in type 2 diabetes."

Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes: Metabolic and antiatherogenic consequences

Miura Y, Yamamoto N, Tsunekawa S, Taguchi S, Eguchi Y, et al.
Diabetes Care 2005; 28 (3): 757–758
Clinical study [English]
Nagoya University School of Medicine, Nagoya, Japan

Adis evaluation

Study messages

Metabolic Effects: Telmisartan has additional beneficial effects on insulin resistance and the development of atherosclerosis in hypertensive patients with type 2 diabetes.
Clinical relevance: B

Study objective

Angiotensin II type 1 receptor blockers (ARBs) have been shown to restore impaired intracellular insulin signalling and reduce the incidence of type 2 diabetes. Among ARBs, telmisartan has been shown to have the unique property of activating peroxisome proliferator-activated receptor-γ (PPAR-γ).
This study evaluated the effects of telmisartan on insulin resistance and circulating levels of adiponectin and highly-sensitive C-reactive protein (hs-CRP) in hypertensive patients with type 2 diabetes who had been undergoing treatment with candesartan cilexetil or valsartan.

Study details

Design: prospective
Control: baseline comparison
Phase: III
Location: Japan
Criteria for evaluation: BP, fasting insulin level, fasting glucose level, insulin resistance, proportion of glycosylated haemoglobin (HbA_{1c}), triglyceride levels, cholesterol levels, C-reactive protein
Methods: Patients were treated with valsartan 80 mg/day (n = 11) or candesartan cilexetil 8 mg/day (n = 7) for > 6 months, during which period none of the changes in clinical and biochemical findings occurred. Patients were then changed to telmisartan, and treatment continued for 12 weeks.

Subjects

Type: patients
Number: 18
Gender: male & female
Age: 36–79 (mean 64) years
Indication: hypertension

Treatments

Drug	Telmisartan
Dose	40 mg/day
Route	PO
Frequency	od
Duration	3 months
Status	Launched

Concomitant medication: antihyperglycaemics (sulphonylureas in 13 patients and nateglinide in 2). Three patients were on diet therapy alone to control their diabetes. No patients received glitazones or insulin.

Results

	Baseline patients previously treated with candesartan or valsartan	Telmisartan for 3 months (n = 18)
Fasting insulin level (mU/L)	10.7	8.6[a]
Fasting plasma glucose (mg/dL)	132.5	126.5
HbA_{1c} (%)	6.89	6.79
Serum triglyceride levels (mg/dL)	133.6	118.7[b]
Cholesterol levels (mg/dL)		
Total	197.2	190.5
HDL	47.6	48.5
Serum adiponectin (µg/mL)	6.95	7.97[c]
hs-CRP (mg/dL)	0.154	0.109[b]

HbA_{1c} = proportion of glycosylated haemoglobin; HDL = high density lipoprotein; hs-CRP = highly-sensitive C-reactive protein.
a $p < 0.01$ vs baseline; b $p < 0.05$ vs baseline; c $p < 0.01$ vs baseline.

Systolic and diastolic BP did not change significantly from baseline (treatment with valsartan or candesartan cilexetil).
A reciprocal association between adiponectin and hs-CRP ($r = -0.53$, $p < 0.01$) was demonstrated.

Adverse events

Body weight gain and oedema did not develop.

Conclusions

"Telmisartan has additional effects on insulin sensitivity and antiatherosclerosis, probably via its effects on PPAR-γ. These findings offer a new idea for the drug targeted to defend against type 2 diabetes with accompanying metabolic disorders."

Metabolic syndrome: Two for the price of one

Farley S
Nature Reviews Drug Discovery 2004; 3: 475
Review [English]

Investigation of the PPAR-γ modulating activity of telmisartan

Telmisartan, a widely-prescribed antihypertensive has been shown to have antidiabetic activity by activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ). It has been observed that 1) treatment of hypertensive patients with some angiotensin II type 1 receptor blockers (ARBs) reduces the risk of developing type 2 diabetes, 2) treatment of diabetic patients with drugs that activate PPAR-γ often results in moderate BP reduction and, 3) there is a structural resemblance between the ARB telmisartan and the PPAR-γ ligand pioglitazone. Taken together, these observations prompted a study that showed that only telmisartan, and not other ARBs, caused substantial activation of PPAR-γ at physiological concentrations. Researchers have classified telmisartan as a moderately potent, partial PPAR-γ agonist, compared to full agonists such as pioglitazone.

Furthermore, telmisartan induced several responses characteristic of PPAR-γ activation, including *in vitro* differentiation of adipocytes and selective modulation of genes involved in lipid and carbohydrate metabolism. Treatment with telmisartan 5 mg/kg for 5 weeks reduced serum glucose, insulin and triglycerides in a murine model of insulin resistance. This was accompanied by a 10% attenuation in weight gain, compared with controls and losartan.

Investigations in cells lacking angiotensin II type 1 receptors have shown that telmisartan stimulates PPAR-γ activity independently of angiotensin receptor blockade. It was also shown that activation of PPAR-γ by telmisartan is mediated exclusively through its ligand-binding domain. Additional studies suggest that telmisartan interacts with a region of the ligand-binding domain similar to that occupied by other partial agonists.

Conclusions

"Telmisartan acts on both angiotensin [type 1] receptors and PPAR-γ, and could therefore be a first line of defence against the metabolic syndrome that commonly presages cardiovascular disease and type 2 diabetes." These findings might stimulate the development of next-generation ARBs that are even more potent activators of PPAR-γ. In addition, antidiabetic PPAR-γ ligands might be developed that are less likely to induce fluid retention and oedema than existing treatments.

Analysis of recent papers in hypertension. Telmisartan: an angiotensin II receptor antagonist with selective PPAR-γ activity

Bloch MJ, Basile JN
The Journal of Clinical Hypertension 2004; 6 (8): 466–468
Review [English]
University of Nevada School of Medicine, Reno, Nevada, USA

Introduction

Thiazolidinediones such as pioglitazone and rosiglitazone are insulin-sensitising agents that increase free fatty acid metabolism, glucose utilisation and insulin sensitivity in patients with type 2 diabetes. Their major mechanism of action through proliferator-activated receptor-γ (PPAR-γ) may be shared by telmisartan, an angiotensin II receptor blocker with structural similarities to pioglitazone. This function may allow telmisartan to treat both the haemodynamic and biochemical features of metabolic syndrome without the fluid retention and oedema associated with the currently available PPAR-γ ligands. Furthermore, in initiating PPAR-γ activation, telmisartan might interact with regions of the ligand binding domain not typically engaged by thiazolidinediones in current use.

Supporting data

A cell-based transactivation assay showed that telmisartan was a moderately potent, selective PPAR-γ agonist, activating the receptor to 25–30% of the maximum level achieved with pioglitazone and rosiglitazone. Irbesartan caused slight PPAR-γ activation, while candesartan cilexetil, valsartan, olmesartan medoxomil, eprosartan and losartan had minimal PPAR-γ agonist activity. In addition, only telmisartan induced adipogenesis and influenced the expression of a number of genes involved in adipocyte differentiation.

Telmisartan also attenuated weight gain and modestly improved glucose, insulin and triglyceride levels compared with losartan and placebo in rats fed a high-fat, high-carbohydrate diet.

Conclusions

These findings suggest that telmisartan is a partial agonist for the PPAR-γ receptor and may be associated with attenuation in weight gain as well as reductions in insulin, glucose and triglyceride levels. However, further trials are required to determine if these effects translate to clinical benefits in patients with diabetes or metabolic syndrome.

Telmisartan – killing two birds with one stone

Doggrell SA
Expert Opinion in Pharmacotherapy 2004; 5 (11): 2397–2400
Review [English]
University of Queensland, Queensland, Australia

Introduction

Hypertension affects up to 60% of patients with type 2 diabetes mellitus. Accordingly, a drug that inhibits the renin-angiotensin system (lowering BP) and acts as a proliferator-activated receptor-γ (PPAR-γ) agonist (increasing insulin sensitivity) could be very useful. This review investigated the recent evidence which suggests that telmisartan, an angiotensin II type 1 (AT_1) receptor blocker (ARB) which has been shown to increase insulin sensitivity in an animal model of insulin resistance, is also a PPAR-γ agonist.

ARBs and PPAR-γ agonism

In one study, both telmisartan and irbesartan increased lipid accumulation in mouse 3T3-L1 preadipocytes. The expression of the adipose protein 2 gene, an adipogenic marker, was also increased with telmisartan, and high concentrations of irbesartan and losartan. The effects of telmisartan and irbesartan on PPAR-γ were not mediated by AT_1, as these agents were shown to increase PPAR-γ activity in cells lacking AT_1 receptors.

Another study demonstrated that telmisartan at concentrations of 1 and 5 µmol/L and irbesartan ≥ 10 µmol/L, but not candesartan cilexetil, valsartan, olmesartan medoxomil or eprosartan, induced differentiation in 3T3-L1 pre-adipocytes. In addition, telmisartan increased the expression of the adipogenic marker gene, adipose protein 2, in mouse pre-adipocytes. Telmisartan also increased the expression of the PPAR-γ target genes in human subcutaneous adipocytes and murine muscle myotubes. Furthermore, telmisartan attenuated weight gain and improved glucose, insulin and triglyceride levels compared with losartan and placebo in an animal model of insulin resistance.

A transactivation study using cells from monkey kidney showed that telmisartan 10 µmol/L caused substantial activation of PPAR-γ. No such effect was seen with irbesartan, candesartan cilexetil, valsartan, olmesartan medoxomil or eprosartan.

Molecular modelling showed the activation of PPAR-γ by telmisartan was most likely due to strong hydrophobic interactions with many of the residues from the H3 and H7 helices on the PPAR-γ binding site. Other sartans may be able to interact with the H3 helix only.

Is telmisartan unique?

It has been suggested that telmisartan is unique among ARBs for its PPAR-γ agonism, which has been demonstrated at physiological concentrations. Irbesartan ≥ 10 µmol/L has been shown to promote adipocyte differentiation, a marker of PPAR-γ activation.

Irbesartan has also been shown to increase insulin sensitivity in obese Zucker rats, an animal model of insulin resistance, hyperinsulinaemia, glucose intolerance and dyslipidaemia. This has not been shown for telmisartan. However, Zucker rats do not have an intact leptin signaling system, which appears to be necessary for stimulation of PPAR-γ to be effective. Further investigation is required to determine how irbesartan increases insulin sensitivity in Zucker rats, if it is not via PPAR-γ activation. Whether irbesartan increases insulin sensitivity in fructose-fed rats (as is true of telmisartan) would also be of interest.

Telmisartan as a lead compound?

Telmisartan may have additional value as a lead compound in the development of drugs that retain AT_1-receptor antagonism, yet are full PPAR-γ agonists.

DETAIL will answer some questions

The ongoing Diabetic Exposed to Telmisartan And enalaprIL (DETAIL) study will provide evidence on whether telmisartan is renoprotective in diabetic nephropathy. *[Editorial comment: The DETAIL study has now been published (see N Engl J Med 2004; 351: 1952–61) and confirmed the renoprotective profile of telmisartan in type 2 diabetic nephrophathy.]*

Future clinical trials with telmisartan

The experimental studies already conducted have provided material for many interesting clinical trials with telmisartan in insulin resistance. These trials could answer questions on the effects of telmisartan on glucose, insulin and triglyceride levels in diabetic patients or those with metabolic syndrome, and determine whether the PPAR-γ agonist properties of telmisartan make it better than other sartans in diabetes with and without nepropathy.

Conclusions

Telmisartan is the prototype of drugs that combine an AT1-receptor antagonist and a PPAR-γ agonist, an approach to killing (treating) two birds (conditions) with one stone (pill). To confirm this, "the effect of telmisartan on insulin sensitivity needs to be evaluated in patients with type 2 diabetes, with and without hypertension."

Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin-angiotensin system

Kurtz TW and Pravenec M
Journal of Hypertension 2004; 22 (12): 2253–2261
Review [English]
University of California, San Francisco, California, USA

Considerable interest in the metabolic effects of antihypertensive drugs has been stimulated by growing concerns about the increasing prevalence of the metabolic syndrome and type 2 diabetes.

Antidiabetic role of ACE inhibitors and ARBs

There are indications that angiotensin-converting enzyme (ACE) inhibitors and some angiotensin II receptor blockers (ARBs) may improve insulin sensitivity and decrease the overall risk for type 2 diabetes. A relationship has been suggested between the renin-angiotensin system (RAS) and the pathogenesis of insulin resistance. Interference with the adverse metabolic effects of angiotensin II has been widely assumed to account for the potential antidiabetic properties of ACE inhibitors and ARBs. However, there are indications from recent studies that the beneficial metabolic effects of ACE inhibitors and particular ARBs may go beyond their effects on the renin-angiotensin system.

Recent clinical and preclinical studies have suggested that ACE inhibitors may increase insulin sensitivity and decrease the risk of type 2 diabetes. In particular, ACE inhibitors might improve glucose metabolism through effects on kinin-nitric oxide pathways and the GLUT4 glucose transporter. A number of clinical trials have indicated that angiotensin receptor blockade might have beneficial effects on glucose metabolism. Most of the placebo-controlled trials, however, have not shown an antidiabetic effect of angiotensin receptor blockade. Nor have these trials, all performed with candesartan celexitil, shown beneficial effects on glucose, insulin or triglyceride levels.

Not all ARBs are the same

The metabolic effects of ARBs may not all be the same; some may have greater effects on glucose and lipid metabolism. The ARB telmisartan is a highly lipid soluble, non-tetrazole ARB with a unique chemical nature. Telmisartan has been shown to activate the peroxisome proliferator-activated receptor-γ (PPAR-γ), a target for insulin-sensitising, antidiabetic drugs. It has been demonstrated that telmisartan can function as a partial agonist of PPAR-γ and can influence the expression of PPAR-γ target genes involved in carbohydrate and lipid metabolism. Furthermore, telmisartan has been shown to reduce glucose, insulin and triglyceride levels in rats fed a high-fat, high-carbohydrate diet. These properties suggest telmisartan may have a greater potential than other ARBs to improve the metabolic disturbances often associated with hypertension as part of the metabolic syndrome and/or type 2 diabetes. Indeed, a small-scale clinical trial and a case study have reported improved biochemical features of the metabolic syndrome and diabetes in patients treated with telmisartan, but not with valsartan or eprosartan.

Conclusions

"The identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating ability suggests new opportunities for developing third-generation ARBs and PPARγ activators, with enhanced potential for treating hypertension, diabetes and the metabolic syndrome."

Telmisartan is a promising cardiometabolic sartan due to its unique PPAR-γ-inducing property

Yamagishi S, Takeuchi M
Medical Hypotheses 2005; 64 (3): 476–478
Comment [English]
Kurume University School of Medicine, Kurume, Japan

Introduction

The metabolic syndrome is strongly associated with insulin resistance and consists of factors such as hypertension and hyperlipidaemia. These factors increase the risk for cardiovascular disease (CVD) and type 2 diabetes. Hypertension occurs approximately twice as frequently in patients with diabetes compared with non-diabetic controls. Conversely, hypertensive patients are more likely to develop diabetes compared with normotensive subjects. Furthermore, up to 75% of CVD in diabetic patients can be attributed to hypertension. The primary treatment goals for hypertensive patients with insulin resistance are, consequently, prevention of type 2 diabetes and prevention of cardiovascular events.

Optimal approach to target organ protection

The optimal antihypertensive approach to target organ protection in these patients remains to be clarified. The renin-angiotensin system (RAS) appears to play a pivotal role in the pathogenesis of insulin resistance and CVD in diabetes. Interruption of the RAS with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) has been shown to prevent the onset of diabetes in patients with hypertension, and reduce cardiovascular and renal disease progression in hypertensive diabetic patients. However, whether the insulin-sensitising properties of some ARBs should lead to their recommendation for insulin resistant-hypertensive patients or patients with type 2 diabetes who do not have nephropathy is currently unresolved.

Telmisartan acts as partial PPAR-γ agonist

The ARB telmisartan has recently been found to act as a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ), which influences expression of genes involved in carbohydrate and lipid metabolism. The PPAR-γ ligands pioglitazone and rosiglitazone improve insulin resistance in diabetic patients. There is also increasing evidence that activators of PPAR-γ exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus reducing the risks of atherosclerosis. Because of its unique PPAR-γ-modulating activity, it is hypothesised that telmisartan may become a promising 'cardio-metabolic sartan', targeting both diabetes and CVD in hypertensive patients.

Testing the hypothesis

A number of trials could be designed to test this hypothesis. If telmisartan improves insulin resistance or endothelial dysfunction in an angiotensin II type 1 (AT_1) receptor-deficient animal model, it may exert beneficial cardio-metabolic activity independent of AT_1 receptor antagonism. Furthermore, if these cardio-metabolic actions were blocked by co-administration of a PPAR-γ inhibitor, the unique properties of telmisartan could be attributed to its PPAR-γ-modulating activity.

Other questions to be resolved include whether telmisartan reduces the development of diabetes and CVD in insulin-resistant patients, and are these benefits also observed in patients pretreated with maximal doses of other ARBs? Does co-treatment with an activator of PPAR-γ attenuate the effects of telmisartan in these patients? The answers to these questions would provide further insight into whether the beneficial cardio-metabolic actions of telmisartan could be ascribed to its PPAR-γ-inducing property.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global End point Trial (ONTARGET) has been designed to assess the efficacy of telmisartan alone or in combination with an ACE inhibitor (ramipril) in high-risk patients with coronary, peripheral, or cerebrovascular disease or diabetes.

Conclusions

Clinical studies such as ONTARGET will provide further information on whether telmisartan has a role in improving insulin resistance and subsequently reducing the development of diabetes and cardiovascular disease in high-risk hypertensive patients.