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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1285–1292
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

The dual peroxisome proliferator–activated receptor α/γ agonist tesaglitazar further improves the lipid profile in dyslipidemic subjects treated with atorvastatin

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Received 17 January 2007; accepted 14 May 2007

Abstract

Tesaglitazar (GALIDA; AstraZeneca, Wilmington, DE) is a dual peroxisome proliferator–activated receptor α/γ agonist previously in clinical development for the treatment of glucose and lipid abnormalities associated with type 2 diabetes mellitus and insulin resistance. This study compared the efficacy of tesaglitazar with that of pioglitazone as adjunctive therapy to atorvastatin in subjects with abdominal obesity and dyslipidemia. In this open-label, 3-way crossover study, 58 subjects received atorvastatin 10 mg once daily in a 6-week run-in period, followed by tesaglitazar 3 mg, pioglitazone 45 mg, or placebo, as adjunctive therapy to atorvastatin, in a randomized sequence for 6 weeks each. Serum triglycerides and other lipids, apolipoproteins, glucose, and insulin concentrations were compared between treatments. Tesaglitazar adjunctive therapy reduced serum triglycerides significantly more from baseline (−1.07 mmol/L) than pioglitazone (−0.33 mmol/L; $P = .007$) or placebo (−0.09 mmol/L; $P < .0001$). Tesaglitazar also resulted in significantly greater improvements in free fatty acids, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, low-density lipoprotein particle size, apolipoprotein (apo) B, apo C-III, and the apo B/apo A-I ratio compared with pioglitazone or placebo. Tesaglitazar adjunctive therapy also reduced fasting plasma glucose, fasting plasma insulin, and insulin resistance (homeostasis model assessment index) significantly more than pioglitazone or placebo ($P < .0001$ for all comparisons). Tesaglitazar was generally well tolerated in combination with atorvastatin, but hemoglobin and absolute neutrophil count decreased and serum creatinine increased more with tesaglitazar than with pioglitazone or placebo. These effects, also shown in previous trials, led to the discontinuation of the clinical development of the drug. In conclusion, the addition of tesaglitazar to a background of atorvastatin therapy further improved the dyslipidemia associated with insulin resistance.

1. Introduction

An atherogenic triad, observed in up to 75% of patients with type 2 diabetes mellitus, is a common characteristic of patients with insulin resistance and is often also manifest in those with abdominal obesity [1-3]. The atherogenic lipid triad comprises raised plasma triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), and a preponderance of small dense low-density lipoprotein (LDL), all of which are associated with an increase in cardiovascular disease (CVD) risk [4-7]. Hydroxymethyl-glutaryl-coenzyme A reductase inhibitors (statins) effectively lower plasma LDL cholesterol (LDL-C) but do not optimize all of the lipid abnormalities associated with increased CVD risk. Therefore, other therapies are required to further improve the atherogenic dyslipidemia typical of insulin resistance.

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0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.05.003

Peroxisome proliferator–activated receptors (PPARs) are nuclear hormone receptors that control the expression of genes involved in carbohydrate and lipid metabolism. Activation of PPARα (eg, by fibrates) stimulates the uptake and catabolism of fatty acids, promotes lipoprotein lipase–mediated lipolysis, and enhances HDL synthesis, resulting in reductions in plasma TGs and increases in plasma HDL-C [8,9]. Modulation of PPARγ (eg, by thiazolidinediones) reduces insulin resistance and enhances peripheral glucose utilization [8]. Integrating both PPARα and PPARγ agonism may result in greater improvements in both lipid and glucose abnormalities of type 2 diabetes mellitus compared with selective PPAR agonism.

Tesaglitazar is a dual PPARα/γ agonist that improved glucose control and the atherogenic dyslipidemia of subjects with insulin resistance and of those with type 2 diabetes mellitus [10,11]. Its clinical development was discontinued because of a benefit-risk profile that did not provide a significant advantage over existing antidiabetic therapies. However, tesaglitazar had been shown to dose-dependently reduce fasting TGs and non–HDL-C, and increase HDL-C and the proportion of larger, less atherogenic LDL particles in patients with manifestations of insulin resistance [10]. Similarly, tesaglitazar treatment reduced TGs, apolipoprotein (apo) B, non–HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and total cholesterol (TC), and increased HDL-C levels in patients with type 2 diabetes mellitus [11]. The present study investigated the effects of tesaglitazar on lipid and glucose metabolism when added to a background of atorvastatin in subjects with raised plasma TGs and abdominal obesity. The effects of tesaglitazar were compared with those of the selective PPARγ agonist pioglitazone.

2. Subjects, materials, and methods

2.1. Study design

This was an open-label, 2-center, randomized, 3-way crossover, placebo-controlled study. Enrolled subjects were given standard diet and lifestyle advice (regarding smoking, alcohol consumption, and physical activity) for the management of dyslipidemia and then entered into a 6-week run-in period of oral atorvastatin 10 mg once daily. After the 6-week run-in period, subjects were randomized to 1 of 6 sequences (ABC, ACB, BAC, BCA, CAB, and CBA) in which they received each of the 3 treatments (A = tesaglitazar 3 mg, B = pioglitazone 45 mg, and C = placebo) as add-on to 10 mg atorvastatin, each given orally once daily in the morning for 6 weeks with no washout period between treatment periods. The follow-up visit was scheduled 3 to 4 weeks after the last day of treatment.

The main objective of the study was to compare the effects of tesaglitazar, pioglitazone, and placebo, given for 6 weeks as adjunctive therapy to atorvastatin, on fasting serum TG concentrations. In addition, assessments of other serum lipid and apolipoprotein concentrations, insulin sensitivity, safety, and tolerability were performed.

2.2. Subject population

Eligible subjects were men and postmenopausal women older than 30 years with abdominal obesity and dyslipidemia (ie, with a high probability of insulin resistance) who had high fasting serum concentrations of TGs (1.7-7.0 mmol/L), LDL-C (≥2.84 mmol/L), and/or TC (≥5.17 mmol/L), and a high waist-to-hip ratio (>0.90 for men and >0.85 for women).

Subjects were excluded if they had serum TGs >7.0 mmol/L, fasting plasma glucose (FPG) >7.0 mmol/L, blood pressure ≥160/95 mm Hg, or hemoglobin (Hb) <120 g/L for men and <110 g/L for women, or if they were at high cardiovascular risk according to the judgment of the investigator. In addition, subjects with serum creatinine >120 μmol/L, serum creatine phosphokinase >3 times the upper limit of normal (ULN), serum albumin <32 g/L, or serum alanine and aspartate aminotransferases >1.5 times ULN were also excluded. Other exclusion criteria included the prior or current concomitant use of insulin or oral antidiabetic agents within 6 months or lipid-lowering agents (other than study treatment with atorvastatin) within 4 weeks, and evidence or history of serious illness or disease. Written informed consent was acquired from each study participant. The study was performed in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee (Region II, Box 1130, 0318 Oslo, Norway). Subject enrollment began in October 2002, and the last subject completed the study in August 2003.

2.3. Laboratory measurements

Blood samples (obtained before breakfast and study medication) were taken at baseline (ie, after the atorvastatin run-in period) and at days 14, 28, 39, and 42 of each treatment period. Hematology and clinical chemistry tests (performed at the Department of Clinical Chemistry, Rikshospitalet-Radiumhospitalet, Oslo, Norway) and urine dipstick analysis (performed at the Lipid Clinic or the Department of Preventive Cardiology, Oslo) were performed using standardized methods.

Lipid concentrations were determined using routine enzymatic colorimetry analysis (Roche/Hitachi 912 auto-analyzer, Mannheim, Germany) at the Department of Clinical Chemistry, Rikshospitalet-Radiumhospitalet. Serum LDL-C concentrations were calculated with the Friedewald equation in subjects with serum TG concentrations ≤4.52 mmol/L or by using the β-quantification method in subjects with TG concentrations >4.52 mmol/L. Serum LDL-C and VLDL-C concentrations were determined after ultracentrifugation of plasma at 105 000*g* for 18 to 22 hours (Beckman Model LE-80K, rotor type 50.4 Ti; Beckman Coulter, Fullerton, CA). Serum HDL-C concentration was determined both directly from serum samples and after ultracentrifugation. Lipoprotein particle

concentration (in nanomoles per liter) and size (in nanometers) were determined from plasma using nuclear magnetic resonance spectroscopy (LipoScience, Raleigh, NC). Serum concentrations of apo A-I, apo B, and apo C-III were measured using immunoturbidimetric assays (Roche/Hitachi 912 autoanalyzer).

Glycosylated hemoglobin (HbA_{1c}) was measured in whole blood. Insulin resistance was calculated using the homeostasis model assessment (HOMA; fasting plasma insulin [FPI] × FPG/7/22.5) [12,13].

2.4. Safety

Adverse events were recorded during the study. Physical examination, electrocardiogram, weight, pulse, and blood pressure were assessed, and blood and urine samples were obtained (for analysis of safety parameters) at the screening visit, after the run-in period with atorvastatin (baseline), after each of the randomized treatment periods, and at the follow-up visit.

2.5. Statistical analysis

A sample size of 52 subjects provided 90% power to detect a 15% difference in change from baseline in fasting serum TG concentrations between tesaglitazar and pioglitazone adjunctive treatments.

Efficacy analysis was based on the completers' analysis set of data. This was defined as those randomized subjects who completed all 3 treatment periods. Mean values for efficacy variables were log-transformed (because of the expected skewed distribution) and analyzed with a mixed-model analysis of variance. The fixed-effect covariates included in the model were baseline, treatment type (tesaglitazar, pioglitazone, or placebo), treatment period (1, 2, or 3), carryover (preceding treatment), replicate (used for efficacy variables that were measured on days 39 and 42 of each treatment period), and a random effect for subject. Efficacy measures were calculated as geometric means and expressed as ratios for statistical comparison: tesaglitazar/pioglitazone and tesaglitazar/placebo. In addition to mean values and standard deviations, 95% 2-sided confidence intervals (CIs) were also presented for the efficacy parameters. Significance was assumed at $P < .05$.

3. Results

3.1. Baseline demographics

Of the 58 subjects (8 women, 50 men) randomized, 51 subjects completed all 3 treatment periods. All subjects were white. Clinical characteristics and lipid variables at screening are presented in Table 1. One subject with an FPG of 9.0 mmol/L at screening, indicating diabetes, was erroneously enrolled and was included in the efficacy analysis.

Seven subjects discontinued the study (3 subjects because of adverse events, 2 because of withdrawn informed consent, 1 because of difficulty in taking blood samples, and 1 death as described below).

Table 1
Clinical characteristics and lipid variables at screening

Men/women (n)	50/8
Age (y)	48 (8)
Body mass index (kg/m^2)	29 (3)
Waist-to-hip ratio	1.01 (0.05)
Systolic blood pressure (mm Hg)	129 (14)
Diastolic blood pressure (mm Hg)	85 (7)
TC (mmol/L)[a]	6.84 (0.92)
HDL-C (mmol/L)[a]	1.14 (0.20)
TGs (mmol/L)[a]	3.33 (1.18)
FPG (mmol/L)[b]	5.54 (0.64)

Values are expressed as mean (SD).
[a] Missing for 1 subject.
[b] Missing for 2 subjects.

3.2. Lipid concentrations

After 6 weeks of treatment, fasting serum TG concentrations were reduced significantly more with tesaglitazar 3 mg adjunctive therapy to atorvastatin (change from baseline ± SD, −1.07 ± 0.94 mmol/L) than with either pioglitazone 45 mg (−0.33 ± 0.85 mmol/L; $P = .007$) or placebo (−0.09 ± 0.75 mmol/L; $P < .0001$; Fig. 2). Tesaglitazar reduced fasting serum TG concentrations from baseline more than pioglitazone or placebo at all assessed time points (days 14, 28, 39, and 42), and maximal treatment effect was evident by day 28 (data not shown). At the end of treatment, TG concentrations with tesaglitazar were 38% lower than with pioglitazone ($P < .0001$; Fig. 1) and 48% lower than with placebo ($P < .0001$; Fig. 2).

Tesaglitazar reduced serum concentrations of TC ($P < .05$) and VLDL-C ($P < .0001$) and the LDL-C/HDL-C ratio ($P < .05$) to a greater extent than pioglitazone (Fig. 1). Total cholesterol ($P = .005$), VLDL-C ($P < .0001$), and LDL-C/HDL-C ratio ($P < .0001$) were also reduced to a significantly greater extent with tesaglitazar than with placebo (Fig. 2). At the end of treatment, serum LDL-C concentrations were not significantly different between the 3 treatments.

At week 6, tesaglitazar significantly increased serum HDL-C concentrations compared with placebo ($P < .0001$ with ultracentrifugation; $P = .008$ measured directly in serum), although in comparison with pioglitazone, only HDL-C concentration measured using the ultracentrifugation method ($P < .002$) was significantly increased (Table 2, Figs. 1 and 2).

3.3. Low-density lipoprotein particle size and concentration

Plasma LDL particle concentrations decreased 10% from baseline after treatment with tesaglitazar, 11% after pioglitazone, and 1% after placebo, but there were no statistically significant differences between the 3 treatments (Figs. 1 and 2). Tesaglitazar produced a significantly greater

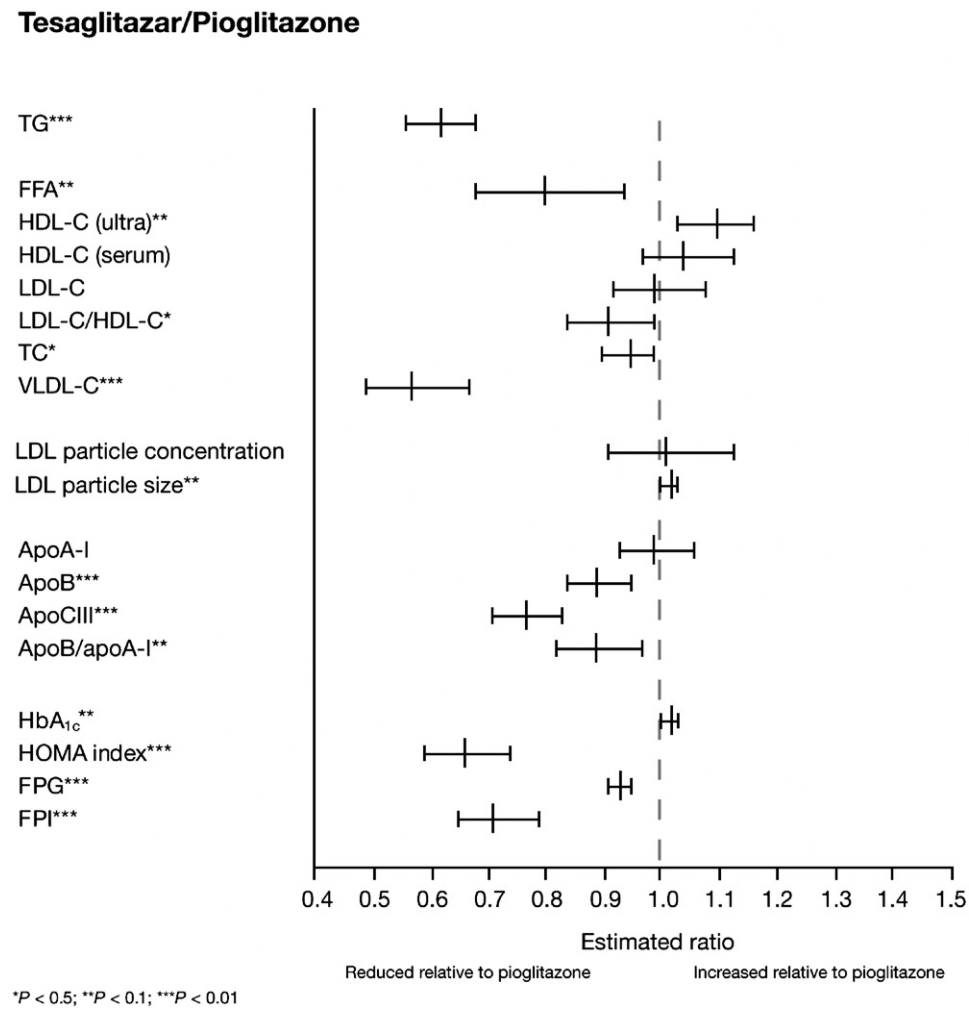

Fig. 1. Changes in lipid, apolipoprotein, and insulin sensitivity variables after 6 weeks of tesaglitazar 3 mg or pioglitazone 45 mg (each given as adjunctive therapy to atorvastatin 10 mg): estimated ratios (with 95% CIs) of tesaglitazar to pioglitazone.

shift from small dense LDL particles to larger, more buoyant LDL particles (ie, toward a less atherogenic phenotype) in comparison with pioglitazone ($P = .01$; Fig. 1) or placebo at 6 weeks ($P < .0001$; Fig. 2).

3.4. Serum apolipoprotein concentrations

Serum concentrations of apo B and apo C-III and the apo B/apo A-I ratio were significantly reduced with tesaglitazar compared with pioglitazone ($P = .0003$, $P < .0001$, and $P = .01$, respectively) or placebo ($P < .0001$, $P < .0001$, and $P = .001$, respectively; Table 2, Figs. 1 and 2). No significant difference in change in serum apo A-I concentrations was observed between treatments.

3.5. Free fatty acid, glucose, and insulin levels

At week 6, plasma concentrations of free fatty acid (FFA) were significantly reduced with tesaglitazar in comparison with either pioglitazone ($P = .007$; Fig. 1) or placebo ($P < .0001$; Fig. 2).

Tesaglitazar reduced the FPG concentration by 9.6%, from a baseline of 5.30 mmol/L, compared with a 2.3% reduction with pioglitazone ($P < .0001$; Fig. 1) and a 3.0% reduction with placebo ($P < .0001$; Fig. 2). At week 6, FPI concentrations were reduced by 47%, from a baseline of 65.9 pmol/L, with tesaglitazar treatment compared with a 20% reduction from baseline with pioglitazone ($P < .0001$) and an 8% reduction with placebo ($P < .0001$). Similarly, 6 weeks of tesaglitazar reduced the HOMA index by 53.4% compared with reductions of 20% with pioglitazone and 14% with placebo ($P < .0001$ for both comparisons; Figs. 1 and 2). Glycosylated hemoglobin levels at week 6 were significantly higher with adjunctive tesaglitazar (5.84%) than with adjunctive pioglitazone (5.73%; $P = .01$; Fig. 1) or placebo (5.67%; $P = .001$; Fig. 2).

3.6. Adverse events

There was no difference in the proportion of subjects experiencing at least one adverse event (55%-60%) across

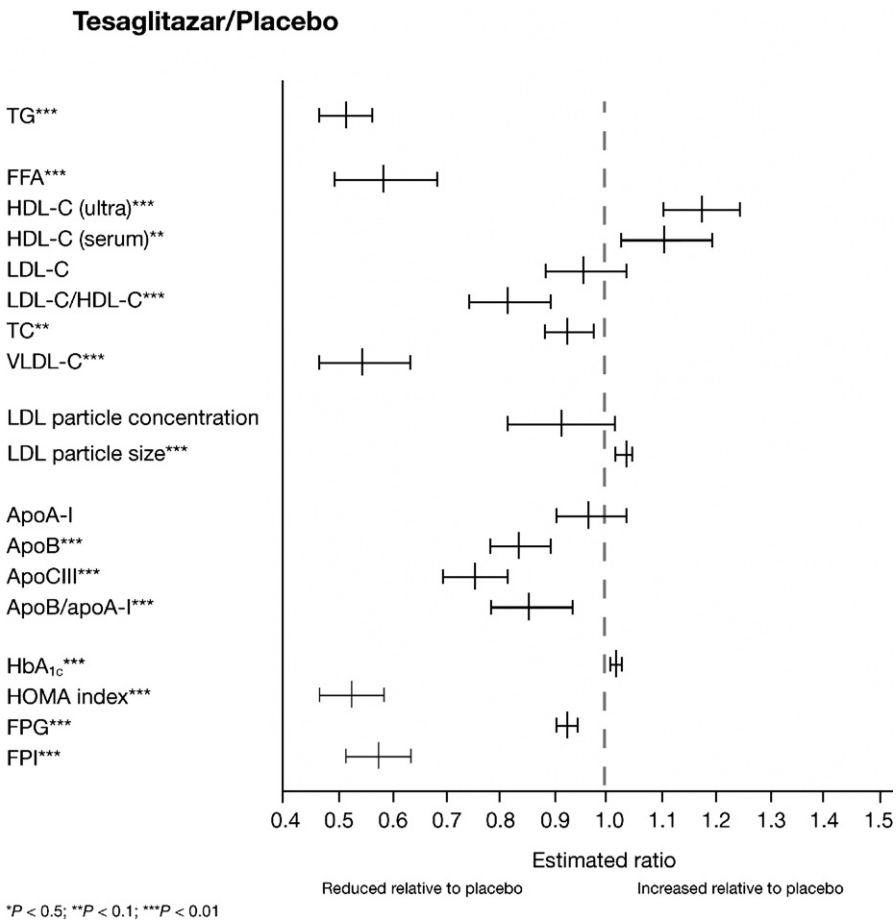

Fig. 2. Changes in lipid, apolipoprotein, and insulin sensitivity variables after 6 weeks of tesaglitazar 3 mg or placebo (each given as adjunctive therapy to atorvastatin 10 mg): estimated ratios (with 95% CIs) of tesaglitazar to placebo.

the 3 treatments. Two subjects reported nonserious myalgia during tesaglitazar treatment. There were 2 adverse event reports of edema, one during tesaglitazar and one during placebo treatment.

There was one death (due to a major postoperative bleed after elective surgery), 2 serious adverse events (back pain during tesaglitazar treatment and chest pain during pioglitazone treatment), and 3 treatment discontinuations (from tesaglitazar) due to adverse events (depression, low absolute neutrophil count [ANC; 1.27×10^9/L], and fatigue).

3.7. Clinical safety variables

Minor decreases in supine blood pressure and pulse were observed with tesaglitazar treatment (change from baseline, −2.7/−2.4 mm Hg and −2.5 beats/min, respectively). Weight increase was apparent after all treatment periods (mean ± SD): tesaglitazar, 0.9 ± 1.7 kg; pioglitazone, 0.8 ± 1.6 kg; and placebo, 0.3 ± 2.2 kg. There were no clinically significant electrocardiographic changes during the study.

3.8. Laboratory safety variables

Absolute neutrophil count and Hb decreased from baseline with all 3 adjunctive treatments, although values at follow-up were within reference ranges (Table 3). In 14 subjects treated with adjunctive tesaglitazar, 9 subjects treated with adjunctive pioglitazone, and 4 subjects treated with placebo, concentrations of Hb were reduced to values less than the reference range (11.6-14.9 g/dL in women, 13.2-16.6 g/dL in men). Reductions in Hb of more than 2 g/dL were observed in 8 subjects receiving tesaglitazar and 4 receiving pioglitazone (Table 3). The ANC was less than 1.5×10^9/L in 7 subjects treated with tesaglitazar, 1 subject treated with pioglitazone, and 2 subjects treated with placebo.

Serum creatinine concentrations increased from baseline to week 6 during treatment with tesaglitazar but not with pioglitazone or placebo (Table 3). The increase in creatinine from baseline was evident at the first assessment (day 14: 103.3 μmol/L in men, 93.9 μmol/L in women), reached a maximum at day 42, and returned to baseline on follow-up. After tesaglitazar treatment, 3 subjects had increases in

Table 2
Concentrations of lipids and apolipoproteins after 6 weeks of treatment with tesaglitazar, pioglitazone, or placebo as adjunctive therapy to atorvastatin

	Baseline (post 6-wk atorvastatin 10 mg run-in), n = 51	Tesaglitazar (3 mg), n = 51	Pioglitazone (45 mg), n = 51	Placebo, n = 51
Lipid variables[a]				
TGs (mmol/L)	2.31 (1.02)	1.24 (0.69)	1.98 (0.85)	2.22 (1.04)
FFA[b] (μmol/L)	391.9 (148.1)	241.7 (109.6)	326.0 (180.6)	398.6 (137.0)
HDL-C (serum[c]; mmol/L)	1.19 (0.3)	1.36 (0.4)	1.31 (0.33)	1.20 (0.24)
HDL-C (ultra[c]; mmol/L)	1.03 (0.2)	1.28 (0.31)	1.20 (0.30)	1.10 (0.23)
LDL-C (mmol/L)	2.68 (0.74)	2.59 (0.69)	2.62 (0.7)	2.74 (0.72)
LDL-C/HDL-C (ultra)	2.69 (0.99)	2.16 (0.86)	2.33 (0.89)	2.57 (0.83)
TC[b] (mmol/L)	4.61 (0.81)	4.39 (0.82)	4.65 (0.77)	4.74 (0.8)
VLDL-C (mmol/L)	0.89 (0.42)	0.54 (0.31)	0.87 (0.44)	0.9 (0.42)
Serum apo A-I (g/L)	1.32 (0.18)	1.47 (0.3)	1.49 (0.25)	1.49 (0.23)
Serum apo B (g/L)	1.06 (0.22)	0.87 (0.23)	0.96 (0.21)	1.03 (0.21)
Serum apo C-III[b] (mg/L)	36.85 (9.85)	30.47 (8.5)	38.69 (8.05)	40.5 (12.39)
Serum apo B/apo A-I ratio	0.82 (0.21)	0.66 (0.44)	0.67 (0.2)	0.7 (0.18)

Values are expressed as means (SD).

[a] All lipid variables were measured in fasting serum samples, with the exception of FFA, which was measured in plasma.

[b] Numbers were less than n = 51: n = 50 for FFA in the pioglitazone group; n = 50 for TC at baseline; for apo C-III, n = 47, 45, 39, and 42 for baseline, tesaglitazar, pioglitazone, and placebo, respectively.

[c] *Serum* refers to direct measurement in serum, whereas *ultra* refers to measurement after ultracentrifugation.

creatinine of more than 50%; but concentrations were back within the reference range at follow-up 3 to 4 weeks after the last dose of study medication. Mean decreases in serum alkaline phosphatase were observed after all 3 treatments, with the largest decreases observed after tesaglitazar (Table 3).

There were no cases of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase elevations to more than 3 times ULN; and bilirubin was never elevated to more than 1.5 times ULN.

4. Discussion

The findings from this study show that tesaglitazar 3 mg, administered as adjunctive therapy to atorvastatin 10 mg, improved a range of abnormalities in plasma lipid and glucose profiles to a greater extent than either pioglitazone or placebo among subjects with abdominal obesity and dyslipidemia (ie, with a high probability of insulin resistance) [4,14].

Dual PPARα/γ agonism with tesaglitazar has previously been shown to be effective in normalizing glucose and lipid abnormalities of type 2 diabetes mellitus and insulin resistance [10,11]. The efficacy of tesaglitazar as adjunctive therapy to a statin has not previously been examined. However, the effect of thiazolidinediones (eg, pioglitazone and rosiglitazone) on a background of statin therapy on the atherogenic lipid profile of type 2 diabetes mellitus and insulin resistance has been investigated [15-18]. In a small, nonblinded study of patients with metabolic syndrome, pioglitazone treatment caused further reductions in TGs and non–HDL-C and increases in HDL-C than statin therapy alone [15]. Similar improvements have been reported in patients with type 2 diabetes mellitus [16].

In the current study, tesaglitazar adjunctive therapy to atorvastatin mediated additional reductions in TGs that were significantly greater than those observed with either adjunctive pioglitazone or placebo. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) treatment guidelines acknowledge that hypertriglyceridemia should be treated with the aim of achieving

Table 3
Hemoglobin, alkaline phosphatase, and creatinine concentrations and ANCs after 6 weeks of treatment with tesaglitazar, pioglitazone, or placebo

		Baseline (post 6-wk atorvastatin 10 mg run-in)	Tesaglitazar (3 mg)	Pioglitazone (45 mg)	Placebo	Follow-up (3-4 wk posttreatment)
Mean values (SD)	Reference range					
Hb, women (g/dL; n = 8)	11.6-14.9	13.45 (0.87)	11.89 (0.58)	12.57 (1.02)	12.87 (0.79)	13.18 (0.80)
Hb, men (g/dL; n = 50)	13.2-16.6	15.04 (0.93)	13.75 (0.98)	14.14 (1.05)	14.54 (0.93)	14.28 (1.05)
ANC (10^9/L; n = 58)	1.8-7.3	3.53 (1.38)	2.58 (0.98)	3.5 (1.57)	3.26 (1.39)	3.2 (1.05)
Creatinine, women (μmol/L; n = 8)	53-97	83.5 (10.3)	107.4 (13.2)	81.4 (16.9)	83.6 (11.7)	79.7 (16.5)
Creatinine, men (μmol/L; n = 50)	71-124	91.90 (10.2)	107.3 (14.9)	94.3 (9.8)	93.0 (13.6)	90.1 (15.1)
Alkaline phosphatase (U/L; n = 58)	70-230	160.9 (39.3)	68.3 (28.5)	108.0 (48.2)	114.7 (54.6)	62.0 (14.3)

Values are expressed as means (SD).

optimal serum TG concentrations of less than 1.7 mmol/L to reduce CVD risk [19,20]. The results of this study indicate that atorvastatin therapy (during the run-in period) reduced fasting serum TGs to a level that would still be considered high according to current guidelines (high TG, 1.7-2.3 mmol/L) [19,20]. The addition of pioglitazone caused an additional small reduction, but only tesaglitazar adjunctive therapy reduced TG concentrations to values less than the NCEP-ATPIII target concentrations. Preclinical studies (in obese Zucker rats) suggest that the antihypertriglyceridemic effects of tesaglitazar are due to decreased hepatic TG production (suggestive of PPARα involvement) and enhanced plasma TG clearance [21]. Consistent with the effects on TGs, reductions in apo C-III were also greater with tesaglitazar adjunctive therapy in comparison with either pioglitazone or placebo adjunctive therapy. Apolipoprotein C-III is an abundant apolipoprotein in human plasma and is expressed on chylomicrons, VLDL, and HDL [22,23]. This apolipoprotein is a modulator of plasma TG metabolism; and its expression inhibits lipoprotein lipase, which is believed to contribute to the development of hypertriglyceridemia [23]. Consequently, the larger reduction in apo C-III levels may partly explain the greater TG-lowering effect of tesaglitazar.

Apolipoprotein B, a component of VLDL, intermediate-density lipoprotein, and LDL, is a marker for atherogenic lipoproteins [2]. Tesaglitazar adjunctive therapy in the present study resulted in significantly greater reductions in fasting serum concentrations of this apolipoprotein than either pioglitazone or placebo adjunctive therapy. The LDL-C concentrations were not significantly reduced after 6 weeks of treatment with atorvastatin by tesaglitazar adjunctive therapy in comparison with either pioglitazone or placebo. Nevertheless, mean LDL-C concentrations were brought to within the optimal range (<2.6 mmol/L) [19,20] at the end of the tesaglitazar adjunctive treatment period (2.59 mmol/L).

It is apparent that both increased LDL particle number and decreased LDL particle size are predictive for CVD risk [5,24]. The current study showed that mean LDL particle size was further increased by the addition of tesaglitazar to atorvastatin, and the largest mean particle diameter was observed after tesaglitazar adjunctive treatment compared with either pioglitazone or placebo. Tesaglitazar has previously been observed to shift the distribution of LDL particles to a less atherogenic phenotype [10]. Such a shift is related to a reduced production of TG-rich VLDL particles [25]. The alterations in lipoprotein particle size with tesaglitazar are likely to be secondary to effects on lipoprotein metabolism (ie, activity of lipoprotein lipase) and are consistent with similar beneficial effects on LDL particle size observed with fibrates [24].

Tesaglitazar adjunctive therapy induced a significantly greater increase in HDL-C levels than pioglitazone adjunctive therapy when HDL-C was measured after ultracentrifugation, but the 2 treatments mediated similar improvements when HDL-C was measured directly in serum. Differences between reported HDL-C concentrations have previously been reported for different methods [26]. However, apo A-I concentrations (the principal apolipoprotein constituent of HDL) were altered to a similar extent with both tesaglitazar and pioglitazone adjunctive treatment. Collectively, these data may indicate that tesaglitazar and pioglitazone adjunctive therapies are similarly effective in raising plasma HDL-C levels.

The present study was performed in nondiabetic subjects with normal HbA_{1c} concentrations and with FPG concentrations within the range 4 - 6 mmol/L. Nevertheless, adjunctive tesaglitazar therapy did reduce FPG, FPI, and the HOMA index of insulin resistance to a greater extent than adjunctive pioglitazone treatment. A minor, statistically significant difference in HbA_{1c} concentrations was observed between treatment periods with tesaglitazar and pioglitazone.

The hematologic findings in the current study (ie, reversible reductions in Hb and ANC) are concordant with observations in other tesaglitazar trials [10,11]. Similarly, dose-dependent increases in serum creatinine have previously been reported with tesaglitazar treatment and, as in the current study, seemed to be reversible on follow-up [10,11]. The mechanisms behind these changes in serum creatinine are unknown; but increases have also been reported with some fibrates, suggestive of possible involvement of PPARα agonism [27,28]. After phase III clinical trials of tesaglitazar 0.5 mg and 1 mg in patients with type 2 diabetes mellitus, the clinical development of tesaglitazar was halted in May 2006. Data showed that its benefit-risk profile was unlikely to give an advantage over currently available therapies, primarily because of renal effects (elevated serum creatinine levels and a reduced glomerular filtration rate).

In summary, the addition of tesaglitazar to atorvastatin mediated additional improvements to the abnormal lipid and glucose profile of subjects with abdominal obesity and dyslipidemia. These findings suggest that dual PPARα/γ agonism has the potential to be effective in reducing CVD risk when used in patients treated with a statin.

Acknowledgments

This research was funded by AstraZeneca.

We thank Lise Bergengen of the Department of Preventive Cardiology for her help with the coordination and technical support of this project. We are also grateful to Ellen Strøm and Inger Ottestad from the Lipid Clinic for their assistance. Additional thanks to Anna Palmer at PAREXEL MMS for provision of medical writing support on behalf of AstraZeneca.

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