Endocrine Journal 2004, **51** (6), 521–527

Addition of Rosiglitazone to Glimepirid and Metformin Combination Therapy in Type 2 Diabetes

EKREM ORBAY, MEHMET SARGIN, HALUK SARGIN, HÜLYA GÖZÜ, OYA UYGUR BAYRAMİÇLİ* AND ALİ YAYLA

Department of Endocrinology and Diabetes, Internal Medicine Clinic, Kartal Education and Research Hospital, Istanbul 34865, Turkey

**Department of Gastroenterology, Internal Medicine Clinic, Kartal Education and Research Hospital, Istanbul 34865, Turkey*

Abstract. The study was planned to determine the efficacy and safety of adding rosiglitazone to a combination of glimepiride and metformin therapy with insufficiently controlled type 2 diabetes. This was an open-label study with a follow-up period of 26 weeks. Thirty patients were taking 3 mg glimepiride two times and 850 mg metformin two times per day. Patients were told to take one rosiglitazone 4 mg tablet before breakfast additionally. The primary efficacy measure was the mean change in HbA_1c from baseline to the end of the study. Secondary efficacy parameters included the mean changes from baseline to the end of the study in fasting plasma glucose (FPG) and insulin levels, as well as total cholesterol, HDL-C, LDL-C, triglycerides, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Mean HbA_1c levels decreased significantly from 7.54 ± 0.9% to 6.57 ± 0.7% ($p<0,001$) at 26th week. FPG levels fell from 169.39 ± 37.8 mg/dl to 135.69 ± 28.0 mg/dl ($p<0.001$), respectively. Insulin levels decreased from 19.60 ± 9.8 U/L to 14.66 ± 11.6 U/L ($p = 0,026$) at 26th week. No one experienced elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than 2.5 times the upper limit of the reference range. This study confirms that the addition of rosiglitazone (4 mg/day) to sulphonylurea and metformin treatment for patients with type 2 diabetes improves glycemic control, is safe, and generally well tolerated.

Key words: HbA_1c, Rosiglitazone, Sulphonylurea, Metformin, Type 2 diabetes mellitus

(*Endocrine Journal* **51**: 521–527, 2004)

TYPE 2 diabetes mellitus is a chronic and progressive disease characterized by impaired insulin secretion and insulin resistance in the liver, adipose tissue and skeletal muscle [1]. These abnormalities all together contribute to abnormal glucose metabolism. The degree and duration of hyperglycaemia is the main reason of chronic complications of type 2 diabetes [2].

Glycemic control with monotherapy cannot be maintained in approximately 10% of patients per year requiring the addition of another antidiabetic drug [3]. Therefore type 2 diabetic patients are often treated with a combination of antidiabetic agents. The need to use drugs with different and complementary mechanisms of action frequently arises in daily clinical practice. There are several reasons to do this: The disease is itself progressive and the therapeutic attempts to achieve and maintain glycemic control often fail in the long term [4, 5]. Some patients do not accept insulin treatment because of the fear of needles and injections, the fear that the complications of diabetes are caused by insulin, and other false beliefs, and instead are ready to take as many antidiabetic pills as prescribed [6].

The most commonly used combination in clinical practice is sulphonylurea and metformin. But when this potent combination is no longer able to achieve glycemic control, the addition of an antidiabetic drug with a different mode of action may lead to improved metabolic control. Sulphonylureas stimulate insulin secretion from the β-cells [7, 8], treating the relative or absolute insulin deficiency rather than the insulin re-

Received: March 30, 2004
Accepted: August 13, 2004
Correspondence to: Mehmet SARGIN, M.D., Çakmak Mah. Soyak Yenişehir Palmiye Sitesi, A-3 Blok D.20 Ümraniye, Istanbul 34770, Turkey

sistance. Metformin lowers glucose by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake [9].

The peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist rosiglitazone acts by increasing insulin sensitivity in adipose tissue, muscle and liver [10]. Rosiglitazone targets insulin resistance by binding to the transcription factor PPAR-γ, thus promoting synthesis of glucose transporters and activating adipocyte differentiation [11, 12]. In addition to reducing insulin resistance, rosiglitazone also improves β-cell dysfunction [13]. Rosiglitazone has been shown to prevent the onset of hyperglycaemia [14] and decrease insulin secretion [15] in animal models of insulin resistance and type 2 diabetes mellitus. The efficacy and safety of rosiglitazone as monotherapy have been established in many studies [16–19].

The mode of action of rosiglitazone and metformin are different but complementary. Consistent with this view, the combined use of metformin and rosiglitazone may be beneficial in patients inadequately controlled by metformin and sulphonylureas. Rosiglitazone has been shown to produce significant improvement in glycemic control when administered to patients who were inadequately controlled on the combination of glibenclamide and metformin [20]. Similar findings were obtained in a trial with troglitazone which was completed before troglitazone was taken off the market because of hepatotoxicity [21].

The aim of the present study was to determine the efficacy and safety of adding rosiglitazone to a combination of glimepiride and metformin therapy with insufficiently controlled type 2 diabetes.

Methods

Study design

In an open-label study, we examined the efficacy of rosiglitazone when added to a therapeutic regimen of glimepiride and metformin in type 2 diabetic patients. Follow-up period of the study was 26 weeks.

Patients

Thirty patients with type 2 diabetes, as defined by the ADA criteria [22], were eligible for the study if they had been receiving glimepiride + metformin therapy for at least 12 months and if their doses had been constant for at least 2 months before the screening visit. They had to be between 40 and 70 years of age and to have a fasting plasma glucose concentration (FPG) between 126 and 270 mg/dl (7 and 15 mmol/l) and hemoglobin A_1c (HbA_1c) levels between 7.0 and 8.0% at screening. All patients gave informed consent according to the Declaration of Helsinki.

Exclusion criteria

Patients were excluded from the study if they had significant renal or hepatic impairment (serum creatinine >1.5 mg/dl or alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin or alkaline phosphatase (AP) >2.5 times the upper limit of the normal laboratory value), hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), anemia (hemoglobin <11 g/dl for men and <10 g/dl for women), New York Heart Association Classification class III or IV cardiac insufficiency, symptomatic diabetic neuropathy, pregnancy or significant abnormalities identified during the screening physical examination, on electrocardiogram (ECG) or in any laboratory tests, including blood chemistry, hematology and urinalysis. Patients requiring insulin therapy, patients who have participated in any rosiglitazone-related study, or have used any investigational drug within 30 days of screening were also excluded.

Treatment

All patients were instructed to take 3 mg glimepiride two times (30 minutes before breakfast and dinner) and 850 mg metformin two times (after breakfast and dinner) per day. Patients were told to take one rosiglitazone 4 mg tablet before breakfast additionally.

Efficacy and safety assessments

All laboratory measurements for efficacy and safety were performed by Dr. Lutfi Kırdar Kartal Education and Research Hospital Laboratories, on blood collected in the fasting state. All of the routine biochemical tests were carried on Roche Diagnostics Modular Systems auto-analyser. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald calculation [23]. Levels of HbA_1c were measured by Roche Diagnostics (RD) immunoturbidimetric assay (cat. no.

1822080); insulin by chemiluminometric immunoassay (DPC-Immulite 2000, cat. no. 152). All subjects who received at least one dose of medication were assessed for clinical safety and tolerability, by physical examination, adverse experience reports, and laboratory safety data. All assessments were performed in the morning so that patients had fasted for at least 9 hours at baseline, at the second week (for rosiglitazone group to estimate hepatotoxicity), at the 13th week, and the end (the 26th week) of the study (or at the withdrawal visit). Patients received their morning doses of study medication after samples had been collected.

The primary efficacy measure was the mean change in HbA_1c from baseline to the end of the study. Secondary efficacy parameters included the mean changes from baseline to the end of the study in FPG and insulin levels, as well as total cholesterol, high density lipoprotein cholesterol (HDL-C), LDL-C, triglycerides, AST and ALT levels.

Safety monitoring included physical examination, vital sign assessment, weight measurements, electrocardiogram, adverse experience query, and laboratory tests. Patients were asked about adverse events using non-leading questions. Investigator rated all adverse events as mild, moderate, or severe and for the relationship to the study drug.

Estimates of insulin sensitivity determined by homeostasis model assessment (HOMA-R) were calculated using FPG and insulin values. HOMA is a mathematical model based on glucose and insulin interaction in different organs, including the pancreas, liver, and peripheral tissues [24].

Statistical analysis

The primary population for efficacy analysis was the intention-to-treat population, those with at least 1 value while receiving therapy (last observation was carried forward in the case of missing data or earlier withdrawals). Efficacy and safety parameters were measured at baseline and after 26 weeks of treatment. The statistical significance was tested by a paired *t* test. Statistical analyses were performed using statistical software (SPSS 11.5). Results are expressed as mean ± SD values. $P<0.05$ was considered significant.

Results

The mean age of 30 patients (17 male, 13 female) was 56.83 ± 9.1 years. Duration of diabetes was 8.53 ± 5.0 years. All of the patients were overweight or obese (BMI: 31.42 ± 4.7 kg/m^2) (Table 1).

Rosiglitazone therapy produced improvements in both glycemic controls (HbA_1c and FPG) between baseline and 26th week. Mean HbA_1c levels decreased significantly from 7.54 ± 0.9% to 6.68 ± 0.7% ($p<0.001$) at 13th week and 6.57 ± 0.7% ($p<0.001$) at the 26th week (Fig. 1). Mean HbA_1c levels decreased after 13th week and then stayed at a steady level. FPG levels fell from 169.39 ± 37.8 mg/dl to 136.39 ± 22.9 mg/dl ($p<0.001$) and to 135.69 ± 28.0 mg/dl ($p<0.001$), respectively. The number of patients who attained an HbA_1c level lower than 6.5% (suggested by ADA) was 17 (8 of them were lower than 6.0%) and 5 of the patients had HbA_1c levels between 6.5% and 7.0%.

Adding rosiglitazone to therapy significantly decreased HOMA-R values. Mean baseline HOMA-R level was 8.54 ± 8.3. Mean HOMA-R levels were calculated as 4.97 ± 4.5 ($p<0.001$) at week 13 and at 5.27 ± 4.4 ($p<0.005$) at week 26 (Fig. 2). Rosiglitazone showed a tendency to reduce levels of circulating insulin. Insulin levels decreased from 19.60 ± 9.8 U/L to 14.62 ± 11.3 U/L ($p = 0.007$) at 13th week and 14.66 ± 11.6 U/L ($p = 0.026$) at 26th week (Fig. 3).

Mean total cholesterol and LDL-C concentrations increased after 26 weeks. Mean levels were 181.28 ± 33.0 mg/dl and 188.26 ± 39.7 mg/dl for total cholesterol and 99.80 ± 25.8 mg/dl and 102.80 ± 29.6 mg/dl for LDL-C, respectively. However, this was accompanied by a rise in HDL-C. Mean HDL-C increased from 44.67 ± 8.0 mg/dl to 48.23 ± 9.9 mg/dl at week 26. As a result, the LDL/HDL ratio fell slightly. Mean triglyceride level was 195.60 ± 102.6 mg/dl at baseline and 189.92 ± 108.8 mg/dl at week 26.

No one experienced elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than 2.5 times the upper limit of

Table 1. Demographic characteristics of patients

n	30
Age (years)	56.83 ± 9.09
Gender (female/male)	13/17
Diabetes Duration (years)	8.53 ± 4.97
HbA_1c (%)	7.54 ± 0.9
BMI (kg/m^2)	31.42 ± 4.7

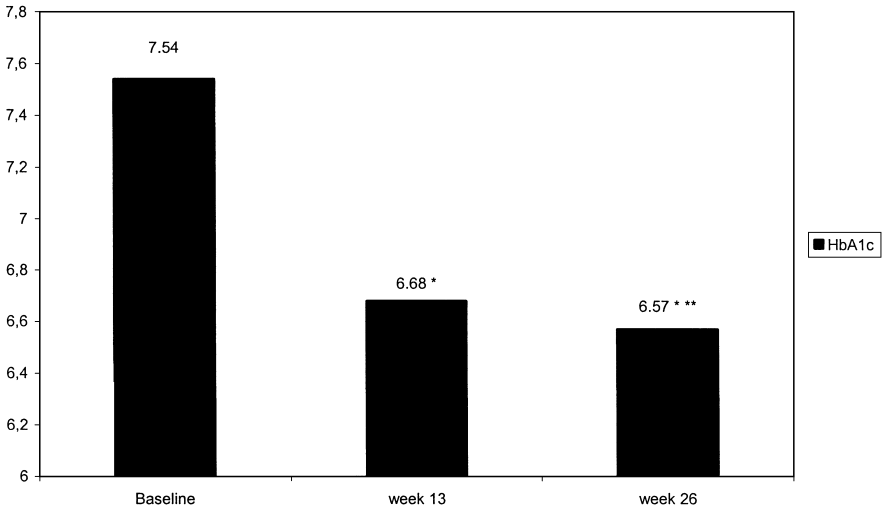

Fig. 1. HbA_1c levels of the patients at baseline, week 13 and week 26
*p<0.001, baseline vs week 13 and week 26
**Non significant, week 13 vs week 26

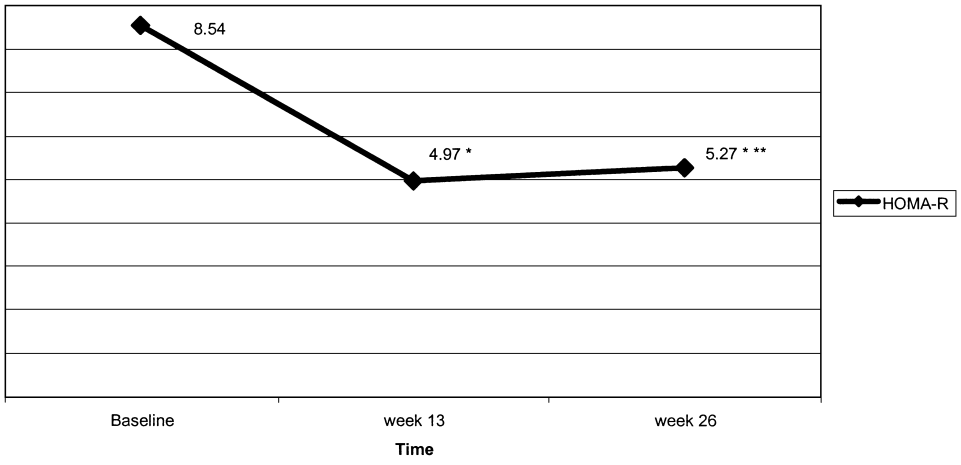

Fig. 2. HOMA-R values of the patients at baseline, week 13 and week 26
*p<0.01, baseline vs week 13 and week 26
**Non significant, week 13 vs week 26

the reference range. Slight decreases were observed in both mean ALT (from 30.07 ± 18.0 mg/dl to 25.00 ± 11.1 mg/dl) and AST (from 23.34 ± 9.0 mg/dl to 22.11 ± 6.4 mg/dl) levels.

Mean changes at total cholesterol, HDL-C, LDL-C, AST, ALT and triglyceride were not statistically significant.

Significant hypoglycemia was not reported in any case. Edema was detected in 3 % of patients. There were no significant changes in vital signs or electrocardiogram parameters in any of the patients.

The mean BMI of patients increased from baseline to 26th week. BMI was calculated as 31.42 ± 4.7 kg/m^2 at baseline, 32.22 ± 4.8 kg/m^2 ($p<0.001$) at week 13 and 32.63 ± 5.3 kg/m^2 ($p<0.001$) at 26th week. There was also a statistically significant increase at BMI between 13th week and 26th week ($p = 0.002$) (Fig. 4).

Discussion

Type 2 diabetic patients are often treated with a combination of antidiabetic agents. The combination of a sulphonylurea with metformin is commonly used in

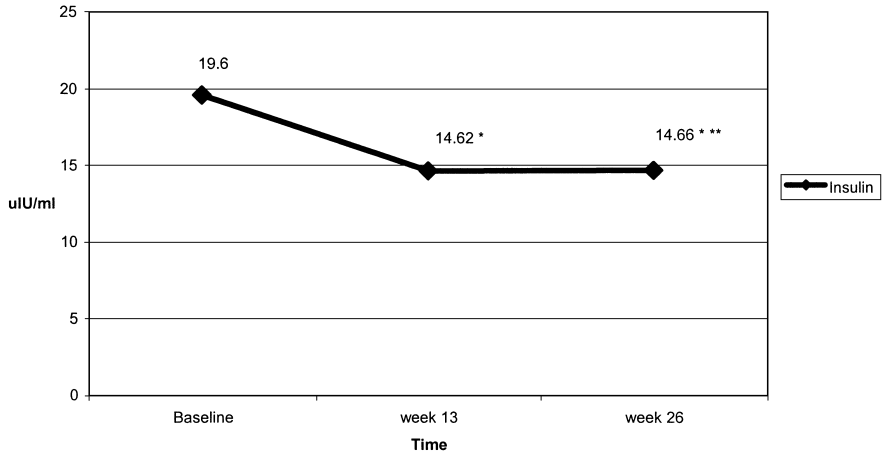

Fig. 3. Insulin levels of the patients at baseline, week 13 and week 26
*p<0.01, baseline vs week 13 and week 26
**Non significant, week 13 vs week 26

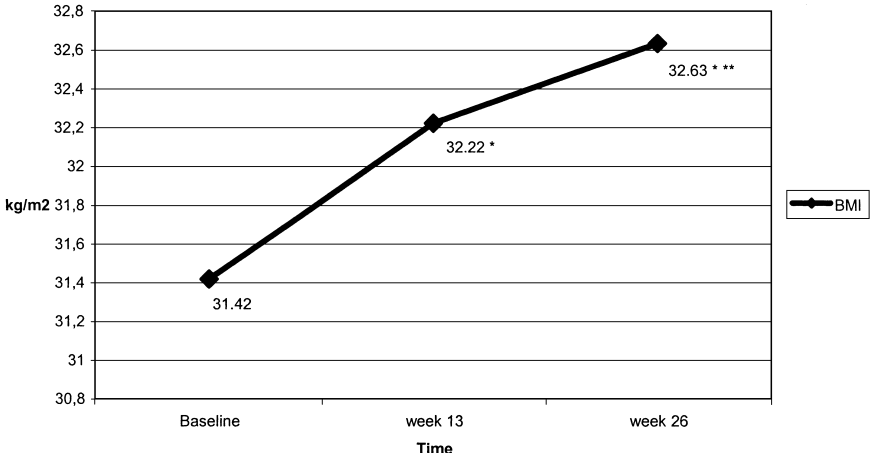

Fig. 4. Body mass index of the patients at baseline, week 13 and week 26
*p<0.001, baseline vs week 13 and week 26
**p<0.01, week 13 vs week 26

clinical practice. Rosiglitazone has been shown to be effective in the treatment of type 2 diabetes either as monotherapy or in combination with other agents. In many of the previous studies rosiglitazone had been added on sulphonylurea or metformin monotherapy alone [18, 25–28], but studies using rosiglitazone in addition to combination therapy are rare [6, 20].

In our study, the decreases in HbA_1c and FPG levels obtained were higher in comparison to the above mentioned triple combination therapy studies [6, 20], whereas other parameters were similar. This may be explained by the difference between the diabetes duration of the study populations. Duration of diabetes in our study was shorter than those of the others.

The complementary actions of combined metformin and rosiglitazone are further supported by the effects of rosiglitazone on insulin sensitivity. Rosiglitazone may provide added therapeutic value by reducing peripheral insulin resistance.

The mean changes in total cholesterol, LDL-C, HDL-C and triglycerides were similar to those observed in previous combination studies of rosiglitazone. Although a small rise in mean LDL-C concentration was observed, this was accompanied by a rise in HDL-C, so the LDL/HDL ratio fell slightly [29].

The weight gain of patients was comparable, but the data presented here demonstrate that the weight gain observed in patients is not associated with an increase

in insulin resistance, and insulin sensitivity improved significantly.

The adverse event profiles were similar to those of studies on rosiglitazone used alone or combination with sulphonylureas or metformin. Lack of laboratory abnormalities associated with rosiglitazone suggests that rosiglitazone was safe and well tolerated. Although hypoglycemia was reported by some patients, this was not serious. The low incidence of edema and absence of clinically significant changes in liver function or ECG were reassuring.

As demonstrated by the UKPDS, the use of sulphonylureas and metformin both alone or in combination in type 2 diabetic patients improves glycemic control and reduces microvascular complications. However, the loss of efficacy over time was associated with persistent insulin resistance and progressive impairment of β-cell function [2]. The management of patients inadequately controlled on combination therapy is a critical step in slowing the progression of the disease and delaying the use of insulin. Additionally, an increase in hyperinsulinaemia may worsen the adverse metabolic and cardiovascular consequences associated with elevated insulin levels that are due to insulin resistance [30]. A more rational approach in these patients may be the reduction of insulin resistance and hyperinsulinaemia [3] by adding an insulin sensitizer such as rosiglitazone.

This study shows that the addition of 4 mg rosiglitazone to existing sulphonylurea and metformin treatment in patients with type 2 diabetes can significantly improve glycemic control as measured by reductions in fasting plasma glucose concentration and the percentage of HbA_1c. The effects of combination drug therapy reflect the efficacy of rosiglitazone. Patients with higher baseline values would be expected to have large reductions in HbA_1c and FPG.

In conclusion, this study confirms that the addition of rosiglitazone (4 mg/day) to sulphonylurea and metformin treatment for patients with type 2 diabetes improves glycemic control, is safe, and generally well tolerated.

References

1. De Fronzo R. Lilly Lecture 1987 (1988) The triumvirate: β-cell, muscle, liver. *Diabetes* 37: 667–687.
2. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with SUs or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853.
3. Scheen AJ, Lefebvre PJ. Oral antidiabetic agents (1998) A guide to selection. *Drugs* 55: 225–236.
4. Turner RC, Cull CA, Frighi V, Holman RR (1999) Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281: 2005–2012.
5. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC (1998) Sulphonylurea failure in non-insulin-dependent diabetic patients over six years: UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 15: 297–303.
6. Kıayıas JA, Vlachou ED, Thedosopoulou E, Lakka-Papadodima E (2002) Rosiglitazone in combination with glimepiride plus metformin in type 2 diabetic patients. *Diabetes Care* 25: 1251–1252.
7. De Fronzo RA (1999) Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131: 281–303.
8. Heine RJ (1996) Role of sulphonylureas in non-insulin-dependent diabetes mellitus part II-'The cons'. *Horm Metab Res* 28: 522–526.
9. Bailey CJ, Turner RC (1996) Drug therapy: metformin. *N Eng J Med* 334: 574–579.
10. Whitcomb RW, Saltiel AR (1995) Thiazolidinediones. *Expert Opin Invest Drugs* 12: 1299–1309.
11. Saltiel AR, Olefsky JM (1996) Thiazolidinediones in the treatment of insulin resistance and type 2 diabetes. *Diabetes* 45: 1661–1669.
12. Smith SA, Cawthorne MA, Coyle PJ, Holder JC, Kirkham D, Lister CA, Murphy GJ, Young PW (1993) BRL 49653C normalizes glycemic control in Zucker fatty fa/fa rats by improving hepatic and peripheral tissue sensitivity to insulin. *Diabetologia* 36 (suppl 1): A184.
13. Matthews DR, Bakst A, Weston WM, Hemyari P (1999) Rosiglitazone decreases insulin resistance and improves beta-cell function in patients with type 2 diabetes. *Diabetologia* 42: A228.
14. Smith S, Lister C, Hughes M, Buckhingham R (1997) The PPAR-γ agonist, BRL 49653, prevents onset of hyperglycemia and proteinuria in ZDF rats. *Diabetes* 46: 150A.
15. Smith S, Boam D, Bretherton-Watt D, Cawthorne MA, Moore G, Loughborough S (1998) Rosiglitazone increases pancreatic islet area, density and insulin content, but not insulin gene expression. *Diabetes* 47: A18.

16. Patel J, Miller E, Hu J (1999) Rosiglitazone monotherapy improves glycemic control in patients with type 2 diabetes. *Diabetes Obes Metab* 1: 165–172.
17. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI (2001) Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 86: 280–288.
18. Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan R (2000) Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycemic control in type 2 diabetic patients. *Diabet Med* 17: 40–47.
19. Lebovitz H, Salzman A (1999) Rosiglitazone safety update. *Diabetes* 49: A39.
20. Jones N, Jones T, Menci L, Xu J, Freed M, Kreider M (2001) Rosiglitazone in combination with glibenclamide and metformin is effective and well tolerated in type 2 diabetes patients. *Diabetologia* 44 (Suppl 1): A904 (Abstract).
21. Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL (2001) The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulphonylurea and metformin: a multicenter randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 134: 737–745.
22. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) *Diabetes Care* 20: 1183–1197.
23. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 18: 499–502.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412–419.
25. Vongthavaravat V, Wajchenberg BL, Waitman JN, Quimpo JA, Menon PS, Ben Khalifa F, Chow WH; 125 Study Group (2002) An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. *Cur Med Res Opi* 18: 456–461.
26. Fonseca V, Rosenstock J, Patwardhan R, Salzman A (2000) Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA* 283: 1695–1702.
27. Gomez-Perez FJ, Fanghänel-Salmón G, Antonio Barbosa J, Montes-Villarreal J, Berry RA, Warsi G, Gould EM (2002) Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. *Diabetes Metab Res Rev* 18: 127–134.
28. Jones TA, Sautter M, Van Gaal LF, Jones NP (2003) Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diab Obes Metab* 5: 163–170.
29. Betteridge DJ (1999) Diabetic dyslipidaemia. *Eur J Clin Invest* 29 (Suppl 2): 12–16.
30. Balkau B, Eschwege E (1999) Insulin resistance. An independent risk factor for cardiovascular disease? *Diab Obes Metab* 1: 23–31.