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Rosiglitazone/Metformin

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Contents

Abstract

▲ The thiazolidinedione rosiglitazone and the biguanide metformin are effective antihyperglycaemic agents with different modes of action; rosiglitazone primarily increases insulin sensitivity, whereas metformin primarily reduces hepatic glucose output.

▲ Antihyperglycaemic combination therapy is often required to achieve effective glycaemic control. A fixed-dose formulation of rosiglitazone/metformin was recently approved in the EU and the US for the treatment of type 2 diabetes mellitus in patients inadequately controlled on metformin monotherapy.

▲ Bioequivalence between the fixed-dose combination tablet and coadministration of rosiglitazone with metformin at the same dosage has been established in a pharmacokinetic study.

▲ Fixed-dose rosiglitazone/metformin 8mg/2g per day reduced glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) levels to a significantly greater extent than metformin 3 g/day in patients with type 2 diabetes in a 24-week, randomised, double-blind study.

▲ Rosiglitazone plus metformin was significantly more effective than metformin alone at reducing HbA_{1c} and FPG levels in patients with type 2 diabetes in three 26-week, randomised, double-blind, placebo-controlled studies.

▲ Rosiglitazone plus metformin was generally well tolerated in all studies and had a tolerability profile similar to that of metformin monotherapy. Mild or moderate symptomatic hypoglycaemia was reported in ≤4.4% of rosiglitazone plus metformin recipients.

Features and properties of rosiglitazone/metformin (Avandamet®)	
Indication	
Type 2 diabetes mellitus inadequately controlled with metformin monotherapy	
Mechanism of action	
Antihyperglycaemic	Rosiglitazone primarily increases insulin sensitivity; metformin primarily reduces hepatic glucose output
Dosage and administration	
Recommended maximal daily dosage	Rosiglitazone/metformin 8mg/2g
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile of rosiglitazone and metformin, respectively, after single-dose rosiglitazone/metformin 4mg/500mg in healthy volunteers	
Peak plasma concentration	242 and 1106 ng/mL
Area under the plasma concentration-time curve from zero to infinity	1142 and 7116 ng • h/mL
Terminal elimination half-life	0.95 and 2.97h
Adverse events	
Most frequent	Upper respiratory tract infection, diarrhoea and headache

Type 2 diabetes mellitus is characterised by insulin resistance and impaired pancreatic β-cell function.[1] Insulin resistance in skeletal muscle, liver and adipose tissue leads to a decrease in peripheral glucose uptake and increased hepatic glucose production. In the early stages of the disease, increased insulin secretion can maintain sufficient glucose metabolism as long as β-cell function remains normal.[1,2] However, hyperglycaemia manifests as β-cell function gradually deteriorates, because insulin secretion can no longer compensate for insulin resistance.[1] Diabetes is associated with an increased risk of cardiovascular disease and, if glucose levels are not controlled, macrovascular (e.g. coronary artery disease, stroke and amputation) or microvascular (e.g. retinopathy, renal failure and peripheral neuropathy) complications may ensue.[2,3]

Patients with type 2 diabetes account for 90–95% of diabetic patients.[3] The risk of developing type 2 diabetes increases with age, obesity and lack of physical activity; most patients with this form of diabetes are obese.[3] In many patients, physiological control of blood glucose can be achieved through improved diet and exercise; however, patient adherence to these measures remains low.[3] Thus, in most patients, pharmacological treatment is required.

Metformin, a biguanide antihyperglycaemic that has been used since the late 1950s, lowers both basal and postprandial plasma glucose levels, primarily by decreasing hepatic glucose output via inhibition of gluconeogenesis.[4,5] Rosiglitazone is a member of the relatively new thiazolidinedione class of antidiabetic drugs, and improves glycaemic control primarily by increasing insulin sensitivity in skeletal muscle, liver and adipose tissue.[2] Both of these drugs are used as monotherapy or in combination therapy regimens, although glycaemic control is often best achieved with combination therapy.[6] Because these drugs have different mechanisms of action, combination therapy with rosiglitazone and metformin may result in better glycaemic control than that achieved with monotherapy.[6] Furthermore, a rosiglitazone/metformin fixed-dose combination tablet has the potential to improve patient compliance to treatment via a reduced pill burden.[7-9]

A fixed-dose combination tablet containing rosiglitazone and metformin (Avandamet®)[1] was recently approved in the EU and the US for the treatment of type 2 diabetes in patients inadequately controlled on metformin monotherapy. This review focuses on data relevant to the use of fixed-dose rosiglitazone/metformin in type 2 diabetes.

1. Pharmacodynamic Profile

The pharmacodynamics of rosiglitazone and metformin have been reviewed in detail elsewhere;[4-6,10,11] as such, this section provides only a brief overview.

- Rosiglitazone binds with high affinity to peroxisome proliferator-activated receptor-γ (PPARγ); PPARγ isoforms are found in key target tissues for insulin action, such as liver, adipose and skeletal muscle tissue.[2,6] Activation of PPARγ is thought to result in regulation of the transcriptional activity of target genes that play a role in the control of glucose production, transport and utilisation, and in the regulation of lipids.[6,11,12]
- In patients with type 2 diabetes, rosiglitazone reduces fasting and postprandial endogenous glucose production and postprandial gluconeogenesis, and increases fasting and postprandial glucose clearance.[2] It also decreases fasting plasma insulin levels and increases whole-body insulin sensitivity.[6,13]
- A recent 6-month, randomised, controlled study has shown that rosiglitazone induced a recovery of pancreatic β-cell function, independently of glycaemic control, in type 2 diabetic patients with disease inadequately controlled with glimepiride plus metformin therapy (n = 17).[14] Recent *in vitro* data suggest that rosiglitazone prevents the impairment of human pancreatic islet function, induced by free fatty acids, by preventing the down-regulation of PPARγ2 and insulin messenger RNA expression in pancreatic islets.[15] Additionally, rosiglitazone has been shown to reduce liver fat content, resulting

1 The use of trade names is for product identification purposes only and does not imply endorsement.

in increased insulin clearance, and to increase PPARγ, lipoprotein lipase and adiponectin expression in adipose tissue in a recent, randomised, double-blind, 16-week study in patients with type 2 diabetes (n = 20).[16]

- Rosiglitazone also has positive effects on markers for cardiovascular disease, such as reducing levels of C-reactive protein,[17] matrix metalloproteinase (MMP)-9,[17] tumour necrosis factor-α,[18] serum amyloid A[18] and soluble CD40L[19] in patients with type 2 diabetes with (n = 39)[18,19] or without (n = 357)[17] coronary artery disease. Rosiglitazone has been shown to reduce systolic and diastolic blood pressure in hypertensive diabetic patients with (n = 48)[20] or without (n = 20–74)[13,21-23] dyslipidaemia, and improve endothelial dysfunction,[24,25] exercise capacity[24] and arterial elasticity,[13] and decrease systemic vascular resistance[13] in patients with type 2 diabetes (n = 17–69).

- By contrast, rosiglitazone therapy is associated with increases in bodyweight and body mass index (BMI),[21,26-28] and in low-density lipoprotein (LDL)-cholesterol and total cholesterol levels in type 2 diabetic patients;[20] however, rosiglitazone also increases high-density lipoprotein (HDL)-cholesterol levels, and the LDL- to HDL-cholesterol and total to HDL-cholesterol ratios remain unchanged (see section 3).[6,26] There are a number of long-term studies currently underway to determine the effects of rosiglitazone on actual cardiovascular outcomes, e.g. the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) study.[29]

- The principal action of metformin is thought to be a reduction in hepatic glucose production;[11] in patients with type 2 diabetes, endogenous glucose production is increased by 25–100%.[5] Metformin also improves peripheral glucose uptake in skeletal muscle and adipose tissue, although this may be a secondary effect of decreasing glucose toxicity.[5,30] It may also improve peripheral insulin sensitivity and decrease intestinal glucose absorption.[5] In addition, metformin decreases plasma free fatty acid levels in diabetic patients, which might contribute to the reduced rate of gluconeogenesis seen with metformin therapy; it may also reduce the effect of lipotoxicity on insulin action and insulin secretion by pancreatic β cells.[5,30,31]

- Metformin also has positive effects on cardiovascular risk factors in patients with type 2 diabetes, such as beneficially affecting the serum lipid profiles of both obese and non-obese patients, decreasing bodyweight, decreasing C-reactive protein and lipoprotein(a) levels, and improving endothelial dysfunction.[4,5] Furthermore, long-term metformin monotherapy has been shown to significantly reduce the risk of developing diabetes-related macrovascular outcomes in type 2 diabetic patients.[5,11]

- Additive effects with rosiglitazone plus metformin on markers for cardiovascular risk were reported in a 24-week, randomised, double-blind study in 90 patients with type 2 diabetes.[32] MMP-9 and plasminogen activator inhibitor-1 (PAI-1) levels decreased by ≈14% and 33%, respectively, with rosiglitazone 8 mg/day plus metformin 1 g/day, compared with an increase of 22% ($p = 0.009$) and a decrease of 0.6% ($p = 0.021$) with metformin 2 g/day.[32] A significant decrease in PAI-1 levels (by 26.6%; $p < 0.01$ vs baseline) was also seen in patients with type 2 diabetes after 1 year of treatment with rosiglitazone 4 mg/day plus metformin 1.5 g/day in a randomised, double-blind study in 95 patients; PAI-1 levels decreased by 11.4% ($p < 0.05$ vs baseline) in recipients of glimepiride 2 mg/day plus metformin 1.5 g/day.[33]

- Rosiglitazone 4 mg/day plus metformin ≥1 g/day decreased the urinary albumin to creatinine ratio by ≈23% ($p = 0.001$ vs baseline; primary endpoint), compared with a reduction of ≈7% with glibenclamide (glyburide) 5 mg/day plus metformin ≥1 g/day (not significant), in a randomised, double-blind, 8-month study in 389 type 2 diabetic patients with microalbuminuria.[34]

2. Pharmacokinetic Profile

The pharmacokinetics of rosiglitazone and metformin, administered as single agents, are well described and have been reviewed in detail previously.[2,4,6] As such, this section briefly overviews the pharmacokinetics of each agent when adminis-

tered alone, but focuses on two studies that evaluated the pharmacokinetics of each agent when administered together as separate tablets[35] or as a fixed-dose combination tablet.[28,36]

Rosiglitazone

- Following oral administration, rosiglitazone is rapidly absorbed, and has an absolute oral bioavailability of 99%.[2] Maximum plasma concentrations (C_{max}) and the area under the plasma concentration-time curve (AUC) increase dose-proportionally over the therapeutic range.[2] After single-dose administration of rosiglitazone 8mg to healthy, fasting volunteers, C_{max}, AUC from time zero to infinity (AUC_{∞}) and time to C_{max} (t_{max}) were 603 ng/mL, 2930 ng • h/mL and 0.75 hours.[2,37]
- The mean volume of distribution at steady state after oral rosiglitazone 4 or 8 mg/day was 17.9L, and increased linearly with bodyweight in patients with type 2 diabetes.[2] Rosiglitazone is extensively protein bound (99.8%), primarily to albumin. Administration of rosiglitazone with food results in a decreased C_{max} (by ≈20%), although total exposure (AUC) is unaffected; t_{max} is increased to about 3.5 hours.[2]
- Rosiglitazone is extensively metabolised in the liver, predominantly by the cytochrome P450 (CYP) 2C8 isoenzyme, with minor metabolism by CYP2C9. The main metabolites result from *N*-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid.[2] The elimination half-life ($t_{1/2}$) is 3–4 hours, is independent of dose and is unaffected by food. Of the total dose of rosiglitazone, 62% and 23% is excreted in the urine and faeces.[2] The mean oral clearance in patients with type 2 diabetes was 2.48 L/h in men and 2.33 L/h in women, and increased linearly with bodyweight.[2]

Metformin

- Oral metformin is absorbed mainly from the small intestine, and has an absolute oral bioavailability under fasting conditions of 50–60% over the dose range of 0.5–1.5g.[4,6] C_{max} and AUC values with increasing doses of metformin are less than dose proportional because of decreased absorption.[6] C_{max} and AUC values after a single dose of metformin 850mg were 1500–2000 ng/mL and 8900–9600 ng • h/mL; t_{max} was 2–3.3 hours.[2]
- Metformin is widely distributed in most tissues and is negligibly protein bound, although the drug does partition into erythrocytes.[28] The apparent volume of distribution after single-dose metformin 850mg is 654L.[28] Steady-state plasma concentrations are achieved within 24–48 hours, and are generally <1000 ng/mL.[28]
- Metformin does not undergo hepatic metabolism and is excreted unchanged in the urine. Approximately 90% of the dose is excreted via the kidneys within the first 24 hours, predominantly via renal tubular secretion, with a $t_{1/2}$ of ≈6.2 hours.[6,28]

Rosiglitazone/Metformin

The comparative pharmacokinetics of rosiglitazone and metformin administered alone or together as separate tablets has been evaluated in 16 healthy, male volunteers in a randomised, open-label, crossover study.[35] In this study, all volunteers received, in crossover fashion, rosiglitazone 2mg twice daily, metformin 500mg twice daily or rosiglitazone 2mg twice daily plus metformin 500mg twice daily for 4 days; the drugs were administered with meals.[35]

Data from a randomised, open-label, crossover, bioequivalence study, in which the pharmacokinetic parameters of rosiglitazone and metformin administered as a fixed-dose combination tablet were compared with those of rosiglitazone and metformin administered together as separate tablets, have been briefly reported in the manufacturer's prescribing information.[28] Additional data have been obtained from a US FDA review.[36] In this study, 24 healthy male and female volunteers received, in crossover fashion, a single dose of fixed-dose rosiglitazone/metformin 4mg/500mg, fixed-dose rosiglitazone/metformin 1mg/500mg or rosiglitazone 4mg plus metformin 500mg; volunteers received the drugs in a fasted state.[36]

- The mean C_{max} of rosiglitazone after rosiglitazone alone or after coadministration with

metformin was 107 and 106 ng/mL, respectively; t_{max} was 3.0 and 3.3 hours. Values for the AUC from 0 to 12 hours (AUC_{12}) were also similar in the corresponding groups (637 vs 641 ng • h/mL).[35]

- Similarly, rosiglitazone had no effect on the absorption of metformin. Mean C_{max} values for metformin after metformin alone or in combination with rosiglitazone were 917 and 934 ng/mL, and t_{max} values were both 3.5 hours; AUC_{12} values were 6605 and 6709 ng • h/mL.[35]
- Bioequivalence between the fixed-dose combination tablet and coadministration of each drug was established in the other study.[28,36] Following single-dose administration of rosiglitazone/metformin 4mg/500mg, C_{max}, AUC_∞ and t_{max} values for rosiglitazone were 242 ng/mL, 1142 ng • h/mL and 0.95 hours; corresponding values after administration of rosiglitazone plus metformin were 254 ng/mL, 1398 ng • h/mL and 0.57 hours. C_{max}, AUC_∞ and t_{max} values for metformin after administration of rosiglitazone/metformin 4mg/500mg were 1106 ng/mL, 7116 ng • h/mL and 2.97 hours. Corresponding values after administration of rosiglitazone plus metformin were 1135 ng/mL, 7413 ng • h/mL and 2.5 hours. The 90% confidence intervals for C_{max} and AUC_∞ for each drug met the criterion for bioequivalence.[28,36]

Special Patient Populations

- In patients with renal dysfunction, renal clearance of metformin is decreased in proportion to creatinine clearance, resulting in increased plasma concentrations of metformin; metformin is contraindicated in patients with renal impairment.[28,38] Renal impairment has no clinically significant effect on the pharmacokinetics of rosiglitazone.[28,38]
- C_{max} and AUC values of unbound rosiglitazone were 2- and 3-fold higher in patients with moderate-to-severe hepatic impairment than in healthy volunteers, and $t_{1/2}$ was about 2 hours longer; treatment with rosiglitazone should not be initiated in patients with hepatic impairment.[28,38]
- Rosiglitazone pharmacokinetics are similar in elderly and younger patients. However, plasma clearance of metformin is decreased, $t_{1/2}$ is prolonged and C_{max} is increased in elderly patients, most likely because of an age-related change in renal function.

Drug Interactions

- Concomitant administration of rosiglitazone with a CYP2C8 inhibitor has the potential to increase plasma concentrations of rosiglitazone; coadministration of rosiglitazone with gemfibrozil resulted in a 127% increase in rosiglitazone AUC.[28] Conversely, coadministration of rosiglitazone with rifampicin, a CYP2C8 inducer, decreased rosiglitazone AUC by 66%.[28]
- Coadministration of metformin with furosemide resulted in increased metformin plasma C_{max} (22%), blood C_{max} (22%) and blood AUC (15%), but did not result in reduced metformin renal clearance; furosemide C_{max} and AUC were reduced by 31% and 12%, and $t_{1/2}$ was decreased by 32%, although renal clearance was not affected.[28]
- If metformin is coadministered with cationic drugs that are eliminated via renal tubular secretion (e.g. amiloride, digoxin and morphine), there is a potential for an interaction by competing for common tubular transport systems.[28]

3. Therapeutic Efficacy

Glycaemic control with fixed-dose rosiglitazone/metformin or uptitration of metformin monotherapy has been compared in a 24-week, randomised, double-blind, multicentre study in 550 patients with type 2 diabetes inadequately controlled with metformin monotherapy or metformin in combination with an oral non-glitazone.[39] Fixed-dose rosiglitazone/metformin has also been evaluated as initial therapy in 190 treatment-naive patients with poorly controlled type 2 diabetes in a 24-week, noncomparative study.[40] Data from these studies have been presented briefly in a poster[39] and an abstract.[40]

The antihyperglycaemic efficacy of rosiglitazone plus metformin has been compared with that of metformin plus placebo in three 26-week, randomised, double-blind, placebo-controlled, multicentre trials in patients with type 2 diabetes (n = 116–348) inadequately controlled by metformin

alone.[26,27,41] Glycaemic control with rosiglitazone plus metformin or fixed-dose glibenclamide/metformin has also been compared in type 2 diabetic patients in a 24-week, randomised, double-blind, multicentre trial (n = 318).[42] Interim (18-month) glycaemic response data from a substudy (n = 1119) of the randomised, nonblind, multicentre RECORD study are also briefly discussed.[43] Two of the placebo-controlled studies have been fully published,[26,27] whereas results from the other three trials have been presented in abstracts and/or posters.[41-43]

Patients in the fixed-dose, double-blind study had a mean age of 58 years, had type 2 diabetes for a mean of 6 years, a mean BMI of 32 kg/m^2 and a mean glycosylated haemoglobin (HbA_{1c}) level of 7.5%.[39] All patients received single-blind metformin 2 g/day for 4 weeks before being randomised to receive rosiglitazone/metformin 4mg/2g per day or metformin 2.5 g/day for 8 weeks, whereupon the dosages were increased, depending on tolerability, to rosiglitazone/metformin 8mg/2g per day or metformin 3 g/day for a further 16 weeks.[39] Patients in the 24-week, fixed-dose, noncomparative study were treatment naive and had a mean HbA_{1c} level >11% or a fasting plasma glucose (FPG) level >270 mg/dL.[40] These patients received initial treatment with rosiglitazone/metformin 4mg/1g per day; the dosage was then uptitrated in 2mg/500mg increments every 4 weeks to a maximum daily dosage of 8mg/2g.[40]

Patients entering into the placebo-controlled trials were aged 40–80 years, had type 2 diabetes for a mean of ≈7–11 years,[26,27,41] a mean BMI of ≈28–30 kg/m^2, a mean HbA_{1c} level of 8.6–9.7%,[26,41] a fasting C-peptide level of ≥0.8 ng/mL,[26,27,41] and an FPG level of 140–300[26,27] or ≈113–375[41] mg/dL. During 3- to 6-week, open-label, run-in phases to the placebo-controlled studies,[26,27,41] all patients received once-daily metformin titrated to 2.5 g/day; patients were then maintained on metformin 2.5 g/day plus single-blind placebo for 4 weeks. At the end of the maintenance period, patients with inadequate glycaemic control were randomised to receive metformin 2.5 g/day plus once-daily rosiglitazone 4 or 8mg or placebo for 26 weeks,[26] or twice-daily rosiglitazone 2 or 4mg or placebo for 26 weeks.[27,41]

In the trial comparing rosiglitazone plus metformin with glibenclamide/metformin, enrolled patients were aged 24–78 years, had type 2 diabetes for a mean of 5.5 years, a mean BMI of 32 kg/m^2, an HbA_{1c} level >7% but <12% and a mean FPG level of ≈190 mg/dL.[42] After a 1-week run-in phase, during which patients were maintained on the dosage of metformin (≥1.5 g/day) they had been receiving for at least 8 weeks prior to enrolment, patients were randomised to receive rosiglitazone 4 mg/day plus metformin 500 mg/day or glibenclamide/metformin 2.5mg/500mg per day.[42] Dosages in both treatment arms were titrated upwards if FPG levels were ≥126 mg/dL or fructosamine levels were ≥252 μmol/L, to a maximum of rosiglitazone 8 mg/day plus metformin 2 g/day or glibenclamide/metformin 10mg/2g per day.[42]

Patients included in the interim analysis of the RECORD study had a mean age of ≈59 years, had type 2 diabetes for a mean of 7.3 years, a mean BMI of ≈31 kg/m^2, a mean HbA_{1c} level of ≈7.9% and a mean FPG level of ≈178 mg/dL.[43] Prior to enrolment, patients were receiving maximally tolerated/permitted doses of metformin or a sulfonylurea (glibenclamide, glimepiride or gliclazide).[43] Upon entry into the study, metformin recipients were randomised to receive either rosiglitazone (up to 8 mg/day) or a sulfonylurea while continuing metformin therapy; sulfonylurea recipients were randomised to receive either metformin or rosiglitazone while continuing sulfonylurea therapy. If patients had an HbA_{1c} level ≥8.5% during treatment, a third oral antihyperglycaemic was added to the rosiglitazone groups or insulin was added to the metformin plus sulfonylurea groups. Dosages were not reported in the poster.[43]

The primary efficacy variable in six of the studies was change from baseline in HbA_{1c} levels.[26,27,39-42] In two of these studies, patients who achieved a reduction from baseline in HbA_{1c} levels of ≥0.7% were considered to have responded to treatment.[27,41] Other efficacy variables included change from baseline in levels of FPG,[26,27,39-42] total cho-

lesterol, HDL-cholesterol and LDL-cholesterol.[26,27,41] Fonseca et al.[26] also used a homeostasis model assessment (HOMA) to estimate insulin sensitivity (HOMA-S) and β-cell function (HOMA-B) during treatment.

The primary aim of the 6-year RECORD study is to evaluate cardiovascular outcomes. However, the primary aim of the 18-month interim analysis was to demonstrate that the addition of rosiglitazone to metformin or a sulfonylurea was noninferior to the addition of metformin to a sulfonylurea or a sulfonylurea to metformin in reducing HbA_{1c} levels.[43]

Versus Metformin Monotherapy

- Combination therapy with rosiglitazone and metformin (administered as a fixed-dose tablet[39] or as separate formulations[26,27,41]) improved glycaemic control to a significantly greater extent than metformin monotherapy in patients with inadequately controlled type 2 diabetes.
- HbA_{1c} and FPG levels decreased to a significantly ($p < 0.001$) greater extent with fixed-dose rosiglitazone/metformin than with high-dose metformin monotherapy in the 24-week study. At week 24, HbA_{1c} levels were reduced from baseline by 0.39% and 0.17% in the rosiglitazone/metformin 8mg/2g and metformin 3g monotherapy groups; 54.0% and 35.7% of patients in the two treatment groups achieved HbA_{1c} levels of <7%.[39]
- Rosiglitazone plus metformin was significantly more effective than metformin alone at reducing HbA_{1c} levels in three 26-week, placebo-controlled studies (figure 1). Mean HbA_{1c} levels in patients treated with rosiglitazone 4 or 8 mg/day (either once daily[26] or in two divided doses[27,41]) plus metformin 2.5 g/day were reduced from baseline by 0.56–1.2%, compared with increases of 0.3–0.45% in patients receiving metformin alone (figure 1). In all three studies,[26,27,41] HbA_{1c} levels in the rosiglitazone groups decreased after week 4 and plateaued from week 18 until the end of treatment.
- A reduction in HbA_{1c} levels of ≥0.7% was achieved by significantly more recipients of metformin plus twice-daily rosiglitazone 2mg (54.3%[27] and ≈52% [value estimated from a graph][41]) or 4mg (61.1%[27] and ≈53%[41]) than patients who received metformin alone (23.5%, both $p < 0.05$,[27] and ≈17%, p-values not reported[41]). A 1.0% reduction in HbA_{1c} levels was achieved by 32.8%, 37.2% and 7.0% of patients receiving once-daily rosiglitazone 4 or 8mg plus metformin or metformin alone, respectively.[26]

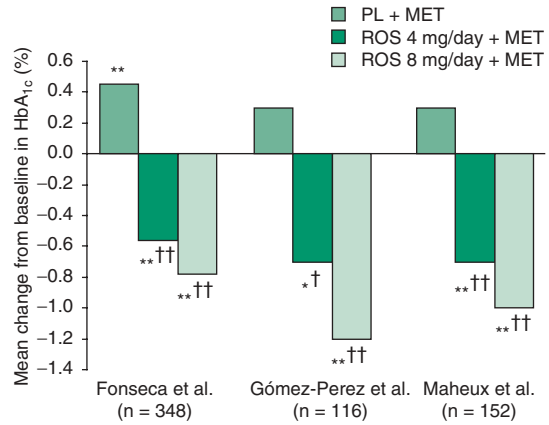

Fig. 1. Effect of rosiglitazone (ROS) plus metformin (MET) compared with MET alone on glycosylated haemoglobin (HbA_{1c}) levels. Changes from baseline in HbA_{1c} levels in patients with type 2 diabetes mellitus. Patients with disease inadequately controlled with MET 2.5 g/day were randomised to receive MET 2.5 g/day plus once-daily ROS 4 or 8mg or placebo (PL) for 26 weeks (Fonseca et al.[26]) or twice-daily ROS 2 or 4mg or PL for 26 weeks (Gómez-Perez et al.[27] and Maheux et al.[41]) in three double-blind, multicentre studies. * $p < 0.01$, ** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.001$ vs PL + MET.

- Rosiglitazone plus metformin was also significantly more effective than metformin alone at reducing FPG levels in the three 26-week, placebo-controlled studies (figure 2). Mean FPG levels in patients treated with rosiglitazone 4 or 8 mg/day (either once daily[26] or in two divided doses[27,41]) plus metformin were reduced from baseline by 33–62.5 mg/dL, compared with increases of ≈2–5.9 mg/dL in patients receiving metformin alone (figure 2). FPG levels in patients treated with rosiglitazone plus metformin decreased during the first 12 weeks of therapy and plateaued until the end of treatment.[26,27,41]
- Mean total cholesterol and LDL-cholesterol levels in recipients of metformin plus once-daily rosiglitazone 4 or 8mg were significantly higher

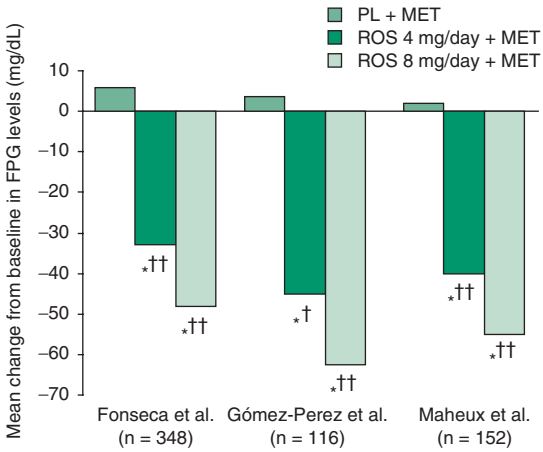

Fig. 2. Effect of rosiglitazone (ROS) plus metformin (MET) compared with MET alone on fasting plasma glucose (FPG) levels. Changes from baseline in FPG levels in patients with type 2 diabetes mellitus. Patients with disease inadequately controlled with MET 2.5 g/day were randomised to receive MET 2.5 g/day plus once-daily ROS 4 or 8mg or placebo (PL) for 26 weeks (Fonseca et al.[26]) or twice-daily ROS 2 or 4mg or PL for 26 weeks (Gómez-Perez et al.[27] and Maheux et al.[41]) in three double-blind, multicentre studies. * $p < 0.001$ vs baseline; † $p < 0.01$, †† $p < 0.001$ vs PL + MET.

than baseline values and corresponding levels in patients who received metformin alone after 26 weeks (figure 3).[26] However, the increase in HDL-cholesterol levels was also significantly higher in the two metformin plus rosiglitazone groups and the total cholesterol to HDL-cholesterol ratios were not significantly different from those at baseline or in the metformin-alone group.[26] Similar results were seen in the two smaller studies.[27,41]

- According to HOMA estimates, insulin sensitivity and β-cell function increased significantly (p-values not reported) in the metformin plus rosiglitazone groups compared with the metformin-alone group, suggesting rosiglitazone may have a role in delaying disease progression.[26] From a median baseline HOMA-S range of 46.6–49.0 units, values increased by 1.7 and 3.8 units in metformin plus rosiglitazone 4 or 8 mg/day recipients compared with recipients of metformin alone. HOMA-B values (median baseline range of 32.5–35.8 units) increased by 10.3–13.7 units with rosiglitazone plus metformin compared with metformin alone.

Versus Metformin in Combination with a Sulfonylurea

- Fixed-dose glibenclamide/metformin was more effective than rosiglitazone plus metformin at reducing HbA_{1c} levels in type 2 diabetic patients in a 24-week study;[42] however, in another study,[43] rosiglitazone in combination with metformin or a sulfonylurea was no less effective than metformin in combination with a sulfonylurea after 18 months of therapy.
- HbA_{1c} levels in recipients of glibenclamide/metformin (mean final dose 7.6mg/509mg) were reduced from baseline by 1.47% compared with a mean reduction of 1.06% ($p < 0.001$) in recipients of rosiglitazone plus metformin (mean final dose 7.1mg plus 1819mg). The percentage of patients who achieved HbA_{1c} levels of ≤7.0% or ≤7.9% was 60% and 87% in the glibenclamide/metformin group and 47% and 79% in the rosiglitazone plus metformin group (statistical analysis not reported). However, a larger proportion of glibenclamide/metformin recipients experienced hypoglycaemia than rosiglitazone plus metformin recipients (section 4).[42]

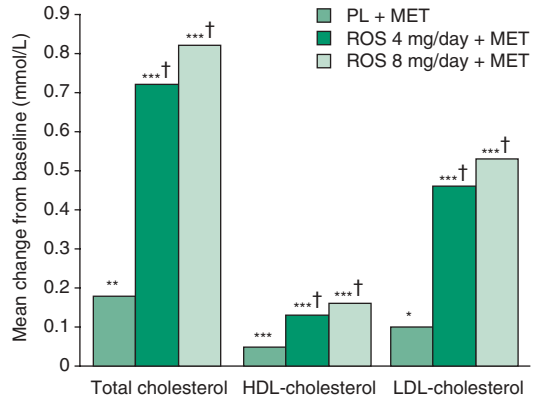

Fig. 3. Effect of rosiglitazone (ROS) plus metformin (MET) compared with MET alone on cholesterol levels. Changes from baseline in total cholesterol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol levels in patients with type 2 diabetes mellitus. Patients with disease inadequately controlled with MET 2.5 g/day were randomised to receive MET 2.5 g/day plus once-daily ROS 4mg (n = 119) or 8mg (n = 113) or placebo (PL; n = 116) for 26 weeks in a double-blind, multicentre study.[26] * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline; † $p < 0.001$ vs PL + MET.

● Mean FPG levels were also reduced to a greater extent with glibenclamide/metformin than with rosiglitazone plus metformin at week 24 (−46 vs −36 mg/dL; p = 0.03).[42]

● Interim (18-month) glycaemic response data from the RECORD study showed that the addition of rosiglitazone to either metformin or a sulfonylurea (glibenclamide, glimepiride or gliclazide) was noninferior to the combination of metformin and a sulfonylurea in reducing HbA_{1c} levels in patients with type 2 diabetes inadequately controlled on metformin or sulfonylurea monotherapy.[43]

● Mean HbA_{1c} levels were reduced by 0.48% and 0.55% in recipients of rosiglitazone plus metformin or a sulfonylurea, compared with reductions of 0.55% and 0.61% when a sulfonylurea was added to metformin or vice versa. Corresponding reductions in FPG levels were also not significantly different between groups (−27, −36, −22 and −29 mg/dL).[43]

As Initial Treatment

● Fixed-dose rosiglitazone/metformin 8mg/2g per day significantly reduced mean HbA_{1c} and FPG levels in treatment-naive patients with poorly controlled type 2 diabetes mellitus in a noncomparative study.[40] By week 24, mean HbA_{1c} and FPG levels had decreased by 4.0% (95% CI −4.30, −3.65) and 139 mg/dL (95% CI −151.0, −127.9) from baseline values of 11.8% and 306 mg/dL, respectively; 38% and 50% of patients achieved an HbA_{1c} level of ≤6.5% and <7%.[40]

4. Tolerability

Tolerability data concerning rosiglitazone plus metformin are reported from two placebo-controlled trials in which patients received rosiglitazone 4 or 8 mg/day either once daily[26] or in two divided doses[27] for 26 weeks, and from the 24-week comparison with glibenclamide/metformin[42] described in section 3.

● Rosiglitazone plus metformin was generally well tolerated in all studies,[26,27,42] and had a tolerability profile similar to that of metformin monotherapy.[26,27] There were no significant between-group differences in the percentage of patients who reported at least one adverse event (69.2–83.8%) in the placebo-controlled studies;[26,27] where reported, the most frequent adverse events were upper respiratory tract infection, diarrhoea and headache.[26] The incidence of gastrointestinal adverse events (e.g. diarrhoea, nausea, vomiting, flatulence and abdominal pain) was similar in recipients of rosiglitazone plus metformin or metformin monotherapy (16.8% vs 15.4%).[27]

● A mean increase in body mass of 0.7 and 1.9kg, respectively, was reported in recipients of once-daily rosiglitazone 4 or 8mg plus metformin 2.5 g/day, compared with a mean decrease in body mass of 1.2kg in patients treated with metformin alone (both p = 0.0001).[26] Oedema was reported in 2.5% and 3.5% of patients in the rosiglitazone groups in this study,[26] compared with 0.9% of the control group (statistical analysis not reported). Oedema was reported in 5.2% of the combined twice-daily rosiglitazone groups, although no patients discontinued treatment because of this adverse event; the incidence of oedema in metformin monotherapy recipients was not reported.[27]

● Mild or moderate symptomatic hypoglycaemia was reported in 2.5%, 4.4% and 1.7% of patients who received once-daily rosiglitazone 4 or 8mg plus metformin or metformin monotherapy, respectively.[26] No significant hypoglycaemia was observed in the other placebo-controlled study.[27] However, hypoglycaemia was reported in 38.4% of glibenclamide/metformin recipients compared with 1.3% of rosiglitazone plus metformin recipients (statistical analysis not reported);[42] 4.4% of glibenclamide/metformin recipients discontinued treatment because of hypoglycaemia compared with no recipients of rosiglitazone plus metformin.[42] Figure 4 illustrates the adverse events occurring in >5% of recipients of glibenclamide/metformin or rosiglitazone plus metformin.

● Apart from one case of bilirubinaemia in a patient who had elevated total bilirubin levels at baseline,[27] no clinically significant changes in ALT, AST, total bilirubin or alkaline phosphatase levels

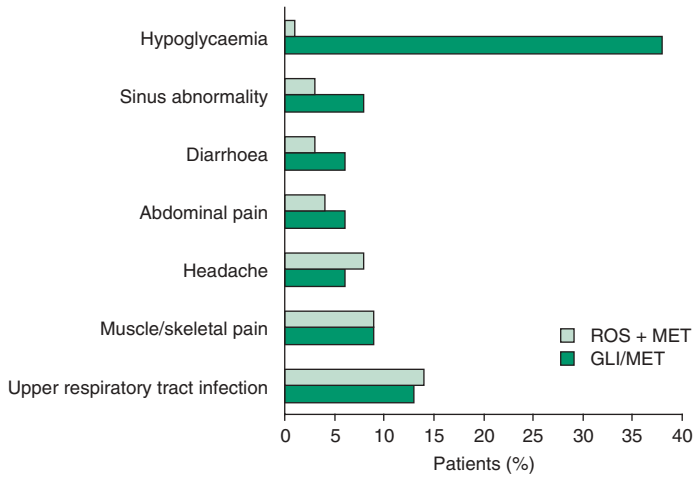

Fig. 4. Tolerability profile of rosiglitazone (ROS) plus metformin (MET) compared with glibenclamide/metformin (GLI/MET) in patients with type 2 diabetes mellitus. Adverse events occurring in >5% of patients. Patients with disease inadequately controlled with MET monotherapy were randomised to receive ROS 4 mg/day plus MET 500 mg/day or GLI/MET 2.5mg/500mg per day for 24 weeks in a double-blind, multicentre trial (n = 318).[42] Dosages in both treatment arms were titrated to a maximum of ROS 8 mg/day plus MET 2 g/day or GLI/MET 10mg/2g per day. Statistical analyses were not reported.

were reported in recipients of either once- or twice-daily rosiglitazone 4 or 8 mg/day.[26,27] There were also no significant changes in ECG parameters.[26,27]

5. Dosage and Administration

In the US, the starting dosage of rosiglitazone/metformin should be based on the patient's current dosage of rosiglitazone and/or metformin. In patients inadequately controlled with metformin monotherapy, the addition of rosiglitazone 4 mg/day to the dose of metformin already being taken is recommended. In patients inadequately controlled with rosiglitazone monotherapy, the addition of metformin 1 g/day to the dose of rosiglitazone already being taken is recommended. The dosage of rosiglitazone/metformin can be increased to no more than rosiglitazone/metformin 8mg/2g per day.[28]

In the EU, the recommended starting dosage is rosiglitazone/metformin 4mg/2g per day. The maximum recommended dosage is rosiglitazone/metformin 8mg/2g per day.[38]

Rosiglitazone/metformin should be taken in two divided doses with meals, with gradual dose escalation.[28,38]

Local prescribing information should be consulted for warnings, precautions and contraindications.

6. Rosiglitazone/Metformin: Current Status

Fixed-dose combination rosiglitazone/metformin is approved in the EU and the US. In the EU, rosiglitazone/metformin is indicated in patients with type 2 diabetes inadequately controlled on metformin alone. In the US, rosiglitazone/metformin is indicated as an adjunct to diet and exercise in patients with type 2 diabetes already receiving a combination of rosiglitazone plus metformin (as separate tablets) or who are inadequately controlled on metformin alone. The fixed-dose combination tablet has been shown to be bioequivalent to the two separate components given concomitantly in a pharmacokinetic study. Fixed-dose rosiglitazone/metformin or rosiglitazone plus metformin has shown clinical efficacy in well controlled trials and was generally well tolerated.

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