Rosiglitazone Maleate and Metformin Hydrochloride in Fixed Combination: What Role in the Treatment of Type 2 Diabetes?

Raymond Farah

Raymond Farah, Specialist in Internal Medicine and Nephrology, Head of the Department of Internal Medicine B, Ziv Medical Center, Safed-Israel. Email: raymond.f@ziv.health.gov.il

Abstract: Traditional first-line intervention in patients with type 2 diabetes and very poor glycemic control is insulin therapy or high doses of sulfonylureas if there is no evidence of volume depletion. This review assesses the efficacy and safety of rosiglitazone and metformin fixed dose combination (avandamet) as initial therapy in patients with uncontrolled type 2 diabetes. This combination therapy achieved significant reduction in A1c and fasting plasma glucose compared with either rosiglitazone or metformin monotherapy as demonstrated by various studies. This combination was generally well tolerated as initial therapy, with no new tolerability issue identified with the fixed-dose combination, with tolerability profile similar to metformin alone. The marked benefit of this combination is the product of the complementary actions of these two agents.

Keywords: type 2 diabetes, rosiglitazone maleate, metformin hydrochloride
Introduction
Type 2 diabetes is a chronic, progressive disease affecting over 18.5 million people in the United States characterized by hyperglycemia usually associated with an increased risk of long-term complications, in particular cardiovascular disease and decreased insulin secretion and insulin sensitivity in liver, adipose tissue, and skeletal muscle.\(^1,2\) Type 2 diabetes is considered one of the most costly diseases in the United States, in part due to its association with microvascular and macrovascular complications.\(^1\) Over 90% of patients with type 2 diabetes are insulin resistant.\(^3\) Intervention trials have provided evidence that strict metabolic control can substantially reduce the burden of the disease. However, in order to accomplish this, the pathogenetic defects must be tackled by appropriate therapy. Insulin resistance not only contributes to impaired glucose homeostasis, but also to the development of dyslipidemia, hypertension, inflammatory response and endothelial dysfunction, thus exacerbating the cardiovascular risk. Improvement of insulin sensitivity can be obtained with metformin and thiazolidinediones. Approximately 50% of patients treated with monotherapy require additional therapy to achieve target glycosylated hemoglobin (HbA\(_{1c}\)) levels 3 years after diagnosis.\(^4\) Currently, there are five main classes of oral antidiabetic medications. The thiazolidinedione (TZD) class of agents targets a core underlying defect of type 2 diabetes, insulin resistance.\(^3\) Rosiglitazone maleate, a member of the thiazolidinedione class of antidiabetic agents that was recently approved by the US Food and Drug Administration, targets insulin resistance by binding to the transcription factor peroxisome proliferator-activated receptor-\(\gamma\), promoting synthesis of glucose transporters and activating adipocyte differentiation.\(^5-7\) In contrast, metformin hydrochloride promotes glucose lowering by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake.\(^8-11\) Because metformin and rosiglitazone act through different mechanisms, their combined use may be indicated in patients whose disease is poorly controlled with a maintenance dose of metformin. This study evaluated the efficacy and safety of adding 4 mg/d and 8 mg/d of rosiglitazone maleate to maximal-dosage of metformin in patients with poorly controlled type 2 diabetes. Combined efficacy was assessed by comparing the level changes in HbA\(_{1c}\), fasting plasma glucose (FPG), fructosamine, serum insulin, free fatty acids (FFA), lipids, lactate, and estimates of insulin sensitivity and \(\beta\)-cell function (BCF) between combined metformin-rosiglitazone treatment and metformin-placebo alone.\(^12,13\) These drugs act through different mechanisms with metformin exerting a prevalent effect on the liver and glitazones improving insulin sensitivity in peripheral tissue. Because of different mechanisms, the association of the two compounds is likely to result in an additive effect. Clinical trials available indicate that the combination of the two drugs results in greater improvement in plasma glucose concentration and HbA\(_{1c}\) as compared to single therapy, without increasing the occurrence of specific side effects. More recently, the two compounds have been associated in the same tablet (avandamet), thus providing the opportunity for a more convenient treatment that may encourage patient compliance and, at the same time, provide a tool to assess whether a more aggressive intervention on insulin resistance may produce favorable effects on the cardiovascular risk.\(^14\)

Mechanism of Action, Metabolism and Pharmacokinetic Profile
Rosiglitazone (avandia) is a selective agonist at the PPAR\(\gamma\) nuclear receptor and reduces glucose by reducing insulin resistance at adipose tissue, skeletal muscle and liver. In animal models rosiglitazone preserved pancreatic islet mass and insulin content and prevented the development of overt hyperglycemia. The glucose lowering effects in clinical trials was gradual in onset with near maximal reductions in FPG following approximately 8 weeks of treatment. Metformin is a biguanide that has antihyperglycemic effects.\(^15\) The main mode of action of biguanides includes a reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis. Other effects delay intestinal glucose absorption and increase insulin sensitivity and glucose uptake into cells, particularly muscle. Metformin stimulates intracellular glycogen synthesis and increases the transport capacity of specific types of membrane glucose transporters.
Rosiglitazone maleate and metformin hydrochloride in fixed combination

(GLUT-1 and GLUT-4). Clinical studies have demonstrated a favorable effect on lipid metabolism independent of its glucose lowering effect.16

Rosiglitazone is used alone (monotherapy) or in combination with a sulfonylurea antidiabetic agent, metformin hydrochloride, or a sulfonylurea and metformin as an adjunct to diet and exercise for the management of type 2 diabetes mellitus. In patients whose hyperglycemia cannot be controlled with a sulfonylurea or metformin alone, rosiglitazone should be added to, not substituted for, sulfonylurea or metformin therapy, as loss of glycemic control may occur. Rosiglitazone is also used in combination with a sulfonylurea and metformin (given separately) in patients who have inadequate glycemic control with a sulfonylurea and metformin. Rosiglitazone in fixed combination with metformin hydrochloride (avandamet) is used as an adjunct to diet and exercise for the management of type 2 diabetes mellitus in patients who have inadequate glycemic control with diet and exercise alone, as second-line therapy in patients who are already receiving therapy with rosiglitazone and metformin separately, or in patients who have inadequate glycemic control with metformin or rosiglitazone monotherapy.17

Rosiglitazone also is used in fixed combination with glimepiride when treatment with combination therapy is appropriate. Rosiglitazone in fixed combination with glimepiride is used as an adjunct to diet and exercise for the management of type 2 diabetes mellitus in patients who have inadequate glycemic control with diet and exercise alone, as second-line therapy in patients who are already receiving therapy with rosiglitazone and glimepiride separately, or in patients who have inadequate glycemic control with glimepiride or rosiglitazone monotherapy. Rosiglitazone may be added to therapy with the fixed combination of glyburide and metformin hydrochloride in patients whose hyperglycemia is not adequately controlled on therapy with the fixed combination. A thiazolidinedione such as rosiglitazone also may be used with repaglinide in patients who have inadequate glycemic control with diet, exercise, and monotherapy with metformin, a sulfonylurea, repaglinide, or a thiazolidinedione. The National Diabetes Data Group and the American Diabetes Association (ADA) currently classify diabetes mellitus as type 1 (insulin dependent, IDDM), type 2 (noninsulin dependent, NIDDM), or that associated with certain conditions or syndromes (e.g. drug- or chemical-induced, hormonal, that associated with pancreatic disease). Type 2 diabetes mellitus previously was described as maturity-onset (MOD) or adult-onset (AODM) diabetes mellitus, since it usually occurs in patients older than 40 years of age. However, type 1 or 2 diabetes mellitus can occur at any age, and the current classification is based on clinical presentation rather than on age of onset. Most individuals with type 2 diabetes mellitus (about 80%–90%) are overweight or obese; obesity itself also contributes to the insulin resistance and glucose intolerance observed in these patients.18–21

Composition and Pharmacokinetic Profile

Avandamet is a fixed dose combination of rosiglitazone and metformin hydrochloride. Two oral strengths are proposed containing 1 mg and 2 mg rosiglitazone (as free base) corresponding to 1.33 mg and 2.65 mg respectively to rosiglitazone maleate combined with metformin hydrochloride. They are presented as film coated tablets. Apart from this difference in strength, the two formulations are identical, excipients include in the tablet core: sodium starch glycollate hypromellose, microcrystalline cellulose, lactose monohydrate, magnesium stearate, and in the film coat: hypromellose, titanium dioxide, macrogol 400, iron oxide yellow/red Film coated tablets are supplied in PVC/PVdC/aluminium blisters.

In a bioequivalence and dose proportionality study of Avandamet 4 mg/500 mg, both the rosiglitazone component and the metformin component were bioequivalent to coadministered 4 mg rosiglitazone maleate tablet and 500 mg metformin HCl tablet under fasted conditions.22–24

Administration of rosiglitazone–metformin (avandamet) 4 mg/500 mg with food resulted in no change in overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in Cmax of both components (22% for rosiglitazone and 15% for metformin, respectively) and a delay in Tmax of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin, respectively). These changes are not likely to be clinically significant. The pharmacokinetics of both the rosiglitazone component and the metformin
component of Avandamet when taken with food were similar to the pharmacokinetics of rosiglitazone and metformin when administered concomitantly as separate tablets with food.

Rosiglitazone (avandia) is a TZD indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes as monotherapy, or in combination with metformin, a sulfonylurea, or insulin when diet, exercise and a single agent do not result in adequate glycemic control rosiglitazone is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycemic control.3

Rosiglitazone (Avandia) targets core defects resulting in significant decreases in insulin resistance and significant improvements in estimates of β-cell function.25

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Maximum plasma concentration (C_max) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range. The elimination half-life is 3–4 hours and is independent of dose. The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metformin is used as a first line treatment of type II diabetes, particularly in overweight people, when diet and exercise have failed to control blood sugar levels. It is also effective in individuals at increased risk of developing type II diabetes, having been shown in the Diabetes Prevention Program to reduce the development of diabetes by 31%.3 In addition to its effect to improve insulin action, metformin may also have a direct effect at the level of the β-cell, where it may counteract the effects of elevated glucose and free fatty acids to decrease β-cell secretory function and viability.12 Many patients with type II diabetes require treatment with more than one antihyperglycemic drug to achieve optimal glycemic control.26,27

The absolute bioavailability of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50%–60%. Studies using single oral doses of metformin HCl tablets of 500 and 1500 mg, and 850–2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg metformin HCl averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24–48 hours and are generally <1 µg/ml. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/ml, even at maximum doses.28,29

Metabolism and Excretion

Avandamet (rosiglitazone maleate and metformin hydrochloride).

Absorption

No statistically significant difference was observed between the absorption characteristics of rosiglitazone and metformin from the avandamet tablet and those obtained from rosiglitazone maleate and metformin hydrochloride tablets, respectively.

Food had no effect on the AUC of rosiglitazone or metformin when avandamet was administered to healthy volunteers. In the fed state, C_max was lower (22% rosiglitazone and 15% metformin) and t_max delayed (by approximately 1.5 h rosiglitazone and 0.5 h metformin). This food-effect is not considered clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of avandamet.

Rosiglitazone

Absorption

Absolute bioavailability of rosiglitazone following both a 4 and an 8 mg oral dose is approximately 99%. Rosiglitazone plasma concentrations peak at around 1 h after dosing. Plasma concentrations are approximately dose proportional over the therapeutic dose range.

Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), although a small decrease in C_max (approximately 20%–28%) and a delay in t_max (approximately 1.75 h) were observed compared to dosing in the fasting state. These small changes are not clinically significant and, therefore, it is not necessary to administer rosiglitazone at any
particular time in relation to meals. The absorption of rosiglitazone is not affected by increases in gastric pH.

**Distribution**
The volume of distribution of rosiglitazone is approximately 14 l in healthy volunteers. Plasma protein binding of rosiglitazone is high (approximately 99.8%) and is not influenced by concentration or age. The protein binding of the major metabolite (a para-hydroxy-sulphate) is very high (>99.99%).

**Metabolism**
Metabolism of rosiglitazone is extensive with no parent compound being excreted unchanged. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulphate and glucuronic acid. The contribution of the major metabolite (a para-hydroxy-sulphate) to the overall antihyperglycemic activity of rosiglitazone has not been fully elucidated in man and it cannot be ruled out that the metabolite may contribute to the activity. However, this raises no safety concern regarding target or special populations as hepatic impairment is contraindicated and the phase III clinical studies included a considerable number of elderly patients and patients with mild to moderate renal impairment.\[^{14,17}\]

*In vitro* studies demonstrate that rosiglitazone is predominantly metabolised by CYP2C8, with a minor contribution by CYP2C9.

Since there is no significant *in vitro* inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A or 4A with rosiglitazone, there is a low probability of significant metabolism-based interactions with substances metabolized by these P450 enzymes. Rosiglitazone showed moderate inhibition of CYP2C8 (IC\(_{50}\) 18 µM) and low inhibition of CYP2C9 (IC\(_{50}\) 50 µM) *in vitro* (see section 4.5). An *in vivo* interaction study with warfarin indicated that rosiglitazone does not interact with CYP2C9 substrates *in vivo*.

**Elimination**
Total plasma clearance of rosiglitazone is around 3 l/h and the terminal elimination half-life of rosiglitazone is approximately 3–4 h. There is no evidence for unexpected accumulation of rosiglitazone after once or twice daily dosing. The major route of excretion is the urine with approximately two-thirds of the dose being eliminated by this route, whereas faecal elimination accounts for approximately 25% of dose. No intact active substance is excreted in urine or feces. The terminal half-life for radioactivity was about 130 h indicating that elimination of metabolites is very slow. Accumulation of the metabolites in plasma is expected upon repeated dosing, especially that of the major metabolite (a para-hydroxy-sulphate) for which an 8-fold accumulation is anticipated.\[^{22}\]

**Special populations**

**Gender:** In the pooled population pharmacokinetic analysis, there were no marked differences in the pharmacokinetics of rosiglitazone between males and females.

**Elderly:** In the pooled population pharmacokinetic analysis, age was not found to influence the pharmacokinetics of rosiglitazone to any significant extent.

**Children and adolescents:** Population pharmacokinetic analysis including 96 pediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the pediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the pediatric population.

**Hepatic impairment:** In cirrhotic patients with moderate (Child-Pugh B) hepatic impairment, unbound C\(_{\text{max}}\) and AUC were 2- and 3-fold higher than in normal subjects. The inter-subject variability was large, with a 7-fold difference in unbound AUC between patients.

**Renal insufficiency:** There are no clinically significant differences in the pharmacokinetics of rosiglitazone in patients with renal impairment or end stage renal disease on chronic dialysis.\[^{11,48}\]

**Metformin**

**Absorption**
After an oral dose of metformin, t\(_{\text{max}}\) is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50%–60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20%–30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that
the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24–48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels \(C_{\text{max}}\) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.\(^8\)\(^-\)\(^10\)

**Distribution**

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean \(V_d\) ranged between 63–276 l.

**Metabolism**

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

**Elimination**

Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.\(^10\)

**Clinical Studies**

There have been no clinical efficacy trials conducted with Avandamet tablets. However, studies utilizing the separate components have established the effective and safe use, and the additive benefit of the combination has been shown in patients with diabetes mellitus inadequately controlled with fasting plasma glucose between 140 and 300 mg/dl despite maximal metformin therapy alone (2500 mg/day).

Bioequivalence of Avandamet with co-administered rosiglitazone maleate tablets and metformin HCl tablets was demonstrated. The addition of rosiglitazone to metformin resulted in significant improvements in glucose concentrations compared to either of these agents alone. These results are consistent with an additive effect on glycemic control when rosiglitazone is used in combination with metformin. No clinical trials have been conducted with combination rosiglitazone and metformin therapy as initial therapy in patients with Type 2 diabetes mellitus. No controlled clinical trials have been conducted in which metformin was added to patients inadequately controlled with rosiglitazone alone.\(^14\)\(^,\)\(^17\) The pattern of LDL-C and HDL-C changes following therapy with rosiglitazone in combination with metformin was generally similar to those seen with rosiglitazone in monotherapy.

**Clinical trials of rosiglitazone add-on therapy in patients not adequately controlled on metformin alone**

A total of 670 patients with Type 2 diabetes participated in two 26 week, randomized, double-blind, and placebo/active-controlled studies designed to assess the efficacy of rosiglitazone in combination with metformin. Rosiglitazone maleate, administered in either once-daily or twice-daily dosing regimens, was added to the therapy of patients who were inadequately controlled on 2.5 g/day of metformin HCl. In one study (1), patients inadequately controlled on 2.5 g/day of metformin HCl (mean baseline FPG 216 mg/dl and mean baseline HbA\(_1c\) 8.8%) were randomized to receive rosiglitazone 4 mg once daily, rosiglitazone 8 mg once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA\(_1c\) was observed in patients treated with the combinations of metformin and rosiglitazone 4 mg once daily and rosiglitazone 8 mg once daily, versus patients continued on metformin alone. A 26 week in the same study, patients with Type 2 diabetes inadequately controlled on 2.5 g/day of metformin HCl who were randomized to receive the combination of rosiglitazone 4 mg twice daily and metformin (\(n = 105\)) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of \(-56\) mg/dl.
and a mean treatment effect for HbA1c of −0.8% over metformin alone.

The combination of metformin and rosiglitazone resulted in lower levels of FPG and HbA1c than either agent alone. Treatment with rosiglitazone (Avandia) as monotherapy resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) in 6 pre-approval double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and 3 placebo-controlled dose-ranging studies of 8 to 12 weeks in duration. Data from pooled clinical trials and their open-label extension studies have shown durable glycemic control with Avandia as monotherapy up to 3½ years.49 In two 26-week, double-blind trials, Avandia in combination with metformin significantly reduced HbA1c and FPG levels compared to metformin alone.25 Additionally, a 24-week, double-blind study demonstrated that Avandia 8 mg/day in combination with submaximal doses of metformin (1000 mg/day) was as effective as uptitrated metformin monotherapy (2000 mg/day) in improving glycemic control, as measured by FPG and HbA1c, and resulted in fewer discontinuations due to gastrointestinal adverse effects. Of note, more patients in the combination group reached an HbA1c < 7% compared to the uptitrated metformin monotherapy group.

Rosiglitazone added to metformin provided sustained HbA1c control for up to 2½ years in an open-label completer analysis. The complementary actions of combined metformin and rosiglitazone is further supported by the effects of rosiglitazone on insulin sensitivity despite maximum doses of metformin. Rosiglitazone may provide added therapeutic value by reducing peripheral insulin resistance. While HOMA-S is an indirect method for determining insulin sensitivity, these results are consistent with glucose-clamp studies using other thiazolidinedione drugs.30,31 The improvements in HOMA-B with metformin-rosiglitazone treatment (not observed with metformin alone) were unexpected and introduce an important potential therapeutic benefit of rosiglitazone. Although the exact mechanism underlying this improvement remains to be determined, rosiglitazone-mediated reductions in glucotoxicity32 and lipotoxicity secondary to elevated concentrations of circulating FFA or both are candidate mechanisms by which rosiglitazone may improve BCF. The effects of rosiglitazone on BCF and insulin sensitivity are consistent with its effects on long-term glycemic control and suggest that it may possibly delay or prevent disease progression.33,34

Despite significant increases in total cholesterol, HDL-C, and LDL-C with the metformin-rosiglitazone treatments, the total cholesterol–HDL-C ratio, which did not change significantly, may be a better predictor of cardiovascular outcome than either total cholesterol or HDL-C levels alone.35,36 Since this study was not designed to assess long-term lipid effects, the long-term significance of these changes is unknown; however, patients with baseline plasma LDL-C levels lower than 3.37 mmol/L (<130 mg/dL) remained less than that level after therapy. No significant changes in triglyceride levels were noted in any treatment group, and segregation of patients into subgroups revealed nonsignificant increases in patients with baseline triglyceride levels lower than 2.26 mmol/L (<200 mg/dL). Among patients in the 8-mg/d rosiglitazone group whose baseline was higher than 2.26 mmol/L (>200 mg/dL), there was a significant statistical decrease observed (64 mg/dL). The clinical significance of lipid level changes may be minimal, because lipid-lowering therapy may be often administered to patients with diabetes irrespective of prior heart disease history.37,38

Elevated FFA may play a role in the development of insulin resistance, because it is associated with increased hepatic glucose output39 and may contribute to β-cell dysfunction via a lipotoxic effect. Elevated FFA has also been linked to endothelial dysfunction and hypertension40 and enhanced platelet aggregation and coagulation, which may increase cardiovascular risk. Therefore metformin-rosiglitazone treatment was significantly more effective in lowering FFA than the metformin alone.41

The weight gain observed in those receiving metformin-rosiglitazone treatment may be attributed to increased adipocyte differentiation, fluid retention, or increased appetite. Despite weight increases, no significant differences in waist-to-hip ratio among groups were observed, suggesting that rosiglitazone treatment leads to increased energy storage in subcutaneous adipose sites that are not associated with increased cardiovascular risk. The small decreases in hemoglobin and hematocrit levels associated with metformin-rosiglitazone therapy may

---

Rosiglitazone maleate and metformin hydrochloride in fixed combination

Clinical Medicine: Therapeutics 2009:1

1221
relate to plasma volume expansion derived from fluid retention and hemodilution. Metformin-rosiglitazone therapy may be a safe alternative therapy to attain optimal glycemic control where monotherapy has failed because the statistically significant decreases in lactate levels associated with metformin-rosiglitazone treatment indicate that rosiglitazone may correct metabolic abnormalities beyond reducing hyperglycemia, and further suggest differing and complementary actions of metformin and rosiglitazone; and ALT elevations greater than 3 times the upper limit of the reference range were not observed in either of the rosiglitazone groups.

Safety and efficacy of rosiglitazone as monotherapy for the management of type 2 diabetes mellitus was established in 6 controlled studies of 8–52 weeks’ duration. Rosiglitazone improved glycemic control as measured by fasting glucose and glycosylated hemoglobin (HbA\textsubscript{1c}) concentrations. Some evidence suggests that rosiglitazone has a more durable glycemic effect than sulfonylureas or metformin. In a long-term (4–6 years’ duration) randomized, controlled clinical trial (A Diabetes Outcome Progression Trial [ADOPT]) evaluating the duration of glycemic control after initiation of monotherapy with rosiglitazone, metformin, or glyburide, the cumulative incidence of treatment failure (i.e. defined as confirmed fasting plasma glucose concentrations exceeding 180 mg/dL on consecutive testing after at least 6 weeks of treatment at the maximum dictated or tolerated dosage of the study drug) at 5 years was 15, 21, and 34%, respectively; this represents a risk reduction with rosiglitazone monotherapy of 32% or 63% compared with metformin or glyburide monotherapy, respectively.\textsuperscript{47} However, the use of fasting glucose concentrations as a measure of treatment failure rather than HbA\textsubscript{1c}, which correlates more closely with diabetic complications, has been criticized; also, differences among the treatment groups in mean HbA\textsubscript{1c} at 4 years were less pronounced, particularly between rosiglitazone and metformin.

Data from a number of comparative trials evaluating combination therapy with rosiglitazone and metformin or a sulfonylurea agent indicate that such combination therapy may result in an additive effect on glycemic control. Efficacy of the combination of rosiglitazone and metformin in patients whose NIDDM was inadequately controlled with metformin alone was established in several controlled studies of 26 weeks’ duration in which combined therapy improved glycemic control without affecting serum insulin concentrations. In patients inadequately controlled with sulfonylurea (e.g. glyburide, glipizide, glimepiride) monotherapy, the combination of rosiglitazone and a sulfonylurea reduced fasting glucose and HbA\textsubscript{1c} concentrations compared with monotherapy with a sulfonylurea alone. The dosages of rosiglitazone, metformin hydrochloride, and the fixed-combination preparation were titrated from an initial dosage of rosiglitazone 2 mg/metformin hydrochloride 500 mg in fixed combination, metformin hydrochloride 500 mg alone, or rosiglitazone 4 mg alone to achieve a mean target daily fasting plasma glucose concentration not exceeding 110 mg/dL or to a maximum dosage of rosiglitazone 8 mg/mefformin hydrochloride 2 g in fixed combination, metformin hydrochloride 2 g alone, or rosiglitazone 8 mg alone. The fixed combination of rosiglitazone and metformin hydrochloride also is used in patients who are inadequately controlled with metformin hydrochloride or rosiglitazone monotherapy. In a controlled clinical trial, concurrent therapy (each agent given separately) with rosiglitazone (4 or 8 mg once daily) and metformin hydrochloride (2.5 g once daily) in such patients reduced mean fasting plasma glucose and HbA\textsubscript{1c} concentrations compared with metformin monotherapy.

No clinical trials have evaluated metformin as add-on therapy in patients inadequately controlled with rosiglitazone monotherapy or the combination of the agents given separately as initial therapy in patients with type 2 diabetes mellitus. In a dose-ranging trial evaluating rosiglitazone 4 or 8 mg as add-on therapy to the maximum daily dosage of metformin hydrochloride, 28.1% of patients receiving the higher dosage of rosiglitazone concurrently with metformin achieved glycated hemoglobin values not exceeding 7%. In patients inadequately controlled with sulfonylurea (e.g. glyburide, glipizide, glimepiride) monotherapy, the combination of rosiglitazone and a sulfonylurea reduced fasting glucose and HbA\textsubscript{1c} concentrations compared with monotherapy with a sulfonylurea alone.

In a 2-year study in geriatric patients (59–89 years of age) who were inadequately controlled on glipizide at half the maximum recommended dosage (10 mg twice
the addition of rosiglitazone (4–8 mg daily) was more effective in preventing loss of glycemic control (defined as fasting plasma glucose concentrations of at least 180 mg/dL, the primary clinical end point) than continued upward titration of glipizide (maximum of 20 mg twice daily). 46,47

However, rosiglitazone or pioglitazone, alone or in combination with other antidiabetic agents, can cause fluid retention as well as other cardiovascular effects and may lead to or exacerbate congestive heart failure (CHF). In addition, several meta-analyses suggest that use of rosiglitazone may be associated with an increased risk of myocardial ischemic events, including angina and myocardial infarction. A similar increased risk of myocardial ischemic events with pioglitazone therapy has not been documented to date; in fact, some data suggest a possible protective effect of pioglitazone on certain cardiovascular outcomes (e.g., death, myocardial infarction, and stroke). However, conclusions about the differences in cardiovascular risk between rosiglitazone and pioglitazone cannot be made in the absence of comparative trials. While data regarding an increased risk of myocardial ischemic events with rosiglitazone therapy are conflicting and inconclusive because of study limitations (e.g., lack of systematic collection of data on cardiovascular events, low cardiovascular event rates, lack of access to original source data, small sample size and short duration of many trials), some experts currently advise against the use of rosiglitazone for the treatment of type 2 diabetes mellitus based on these cardiovascular risks and the availability of other treatment options. Macrovascular risk reduction with rosiglitazone or any other oral antidiabetic agent has not been established. Recent epidemiological studies have suggested that T2DM predisposes patients to an increased risk of a variety of cancer and there is a debate and also concern that the use of insulin as insulin glargine may increase cancer risk. 48,49

No definitive conclusions regarding a possible causal relationship between insulin glargine use and the occurrence of malignancies can be drawn from the results of this study. 50

**Conclusion**

Combination metformin–rosiglitazone treatment is effective and safe in reducing hyperglycemia in patients with type 2 diabetes. In patients whose fundamental abnormality is insulin resistance, such a combination raises the exciting possibility of treating diabetes by targeting the underlying cause of the disease, rather than the traditional approach of stimulating insulin secretion. Nearly 30% of patients taking the combination therapy achieved HbA\textsubscript{1c} levels of 7% or less. This level of glycemic control is 3-fold greater than what was achieved among those taking metformin alone. Insulin resistance is a major endocrinopathy underlying the development of hyperglycaemia and cardiovascular disease in type 2 diabetes. Metformin (a biguanide) and rosiglitazone (a thiazolidinedione) counter insulin resistance, acting by different cellular mechanisms. The two agents can be used in combination to achieve additive glucose-lowering efficacy in the treatment of type 2 diabetes, without stimulating insulin secretion and without causing hypoglycaemia. Both agents also reduce a range of atherothrombotic factors and markers, indicating a lower cardiovascular risk. Early intervention with metformin is already known to reduce myocardial infarction and increase survival in overweight type 2 patients. Recently, a single-tablet combination of metformin and rosiglitazone, (Avandamet), has become available. Avandamet is suitable for type 2 diabetic patients who are inadequately controlled by monotherapy with metformin or rosiglitazone. Patients already receiving separate tablets of metformin and rosiglitazone may switch to the single-tablet combination for convenience. Also, early introduction of the combination before maximal titration of one agent can reduce side effects. Use of Avandamet requires attention to the precautions for both metformin and rosiglitazone, especially renal, cardiac and hepatic competence.

In summary, Avandamet is a single-tablet metformin–rosiglitazone combination that doubles targets insulin resistance as therapy for hyperglycaemia and vascular risk in type 2 diabetes. The combination treatment of metformin and rosiglitazone significantly reduced HbA\textsubscript{1c} and FPG concentrations, in a dose-ordered fashion compared with baseline and with metformin alone. 51,52 Conversely, treatment with metformin alone was associated with significant increases in HbA\textsubscript{1c} concentrations, indicating that these agents complement each other to achieve optimal glycemic control and confirming the
clinical utility of metformin in combination with a thiazolidinedione drug. Additional investigation is needed to determine whether this combination will alter the long-term risk of cardiovascular disease or delay disease progression.

Disclosure

The author reports no conflicts of interest.

References

Rosiglitazone maleate and metformin hydrochloride in fixed combination


Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:
- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

http://www.la-press.com