# *Hypoglycemics, Thiazolidinediones (TZDs) Review*

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### *FDA-Approved Indications*

| Drug | Manufacturer | Indication(s) |
|---|---|---|
| **TZDs** | | |
| pioglitazone (Actos®)[1] | Takeda | Adjunct to diet and exercise, either as monotherapy or in combination therapy with a sulfonylurea, metformin, or insulin, for the treatment of type 2 diabetes mellitus |
| rosiglitazone (Avandia®)[2] | GlaxoSmithKline | Adjunct to diet and exercise, either as monotherapy or in combination therapy with sulfonylurea, metformin, or sulfonylurea plus metformin, for the treatment of type 2 diabetes |
| **TZDs and glimepiride** | | |
| pioglitazone/ glimepiride (Duetact™)[3] | Takeda | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and sulfonylurea combination or who are not adequately controlled on either agent alone |
| rosiglitazone/ glimepiride (Avandaryl®)[4] | GlaxoSmithKline | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with dual rosiglitazone and glimepiride therapy is appropriate |
| **TZDs and metformin** | | |
| pioglitazone/ metformin (Actoplus Met™)[5] | Takeda | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and metformin combination or who are not adequately controlled on either agent alone |
| rosiglitazone/ metformin (Avandamet®)[6] | GlaxoSmithKline | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with dual rosiglitazone and metformin therapy is appropriate |

### *Overview*

It is estimated that 23.6 million Americans have diabetes.[7] The widespread occurrence of obesity supports the projection that cases of diabetes will continue to grow. Diabetes causes a significant economic burden both in terms of direct and indirect costs to society. It is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to

minimize chronic complications including blindness, renal dysfunction resulting in dialysis or transplantation, and nontraumatic amputations.[8]

Three metabolic defects are responsible for the progression to type 2 diabetes mellitus: peripheral insulin resistance, impaired β-cell function, and increased hepatic glucose production.[9] The thiazolidinediones (TZDs) work by decreasing insulin resistance. Combination products of TZDs with metformin and glimepiride have recently been released and may improve adherence for those patients requiring combination therapy.

The 2009 update to the American Diabetes Association (ADA) consensus algorithm divides its treatment recommendations into tier one interventions and tier two interventions.[10] Tier one interventions are those treatment recommendations that are considered well-validated, most clinically- and cost-effective, and represent the preferred pathway of treatment for patients with type 2 diabetes. Tier two interventions are less well-validated options and should be used only in select patient populations. The initiation of metformin concurrent with lifestyle modifications at the time of diagnosis continues to be recommended by the ADA, and is considered step one of three of the tier one recommendations. If metformin therapy and lifestyle interventions fail to achieve or sustain glycemic goals, step two of the tier one recommendations proposes the addition of either basal insulin or a sulfonylurea. In select patient populations who do not respond adequately to the step one interventions and in whom hypoglycemia should be avoided, the clinician may employ a tier two intervention by adding pioglitazone (Actos). The use of rosiglitazone (Avandia) is not a tier one or two recommendation in the treatment algorithm.

The 2007 American Academy of Clinical Endocrinologists (AACE) recommendations for the treatment of type 2 diabetes includes TZDs as a treatment option as well as most of the oral antidiabetic agents.[11] Combining therapeutic agents with different modes of action may be advantageous. The AACE recommends the use of insulin sensitizers such as metformin and/or thiazolidinediones as part of the therapeutic regimen in most patients unless contraindicated or intolerance to these agents has been demonstrated.

## *Pharmacology*

The TZDs bind and activate peroxisome proliferator-activated receptor gamma (PPAR-γ) in skeletal muscle, adipose tissue, and the liver, resulting in improved insulin action by enhancing the sensitivity of peripheral muscle glucose uptake and possibly reducing hepatic glucose production.[12,13] The TZDs require the presence of insulin.

Metformin (Glucophage), a biguanide, decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[14,15]

Glimepiride (Amaryl) is a member of the sulfonylureas, which enhance response of beta cells in the pancreatic islet to glucose, in turn stimulating the release of insulin.[16,17]

### *Pharmacokinetics*

| Drug | Bioavailability (%) | Half-Life (hr) | Metabolites | Excretion (%) |
|---|---|---|---|---|
| glimepiride (Amaryl)[18] | 100 | 5-9.2 | Two inactive metabolites | renal: 60<br>feces: 40 |
| metformin (Glucophage)[19] | 50-60 | 6.2 | None | renal: >90 |
| pioglitazone (Actos)[20] | -- | 3-7 (parent); 16-24 (parent plus metabolites) | M-II, M-III, M-IV (active in animal models) | renal: neglible<br>feces: 70-85 |
| rosiglitazone (Avandia)[21] | 99 | 3-4 | Yes, inactive | renal: 64<br>feces: 23 |

In bioequivalence studies of all combination products, both the TZD and the metformin or glimepiride component were bioequivalent to the single agents administered together.[22,23,24,25]

### *Contraindications/Warnings*[26,27,28,29,30,31]

Pioglitazone (Actos)- and rosiglitazone (Avandia)-containing products have black box warnings stating that their use either alone or in combination with other antidiabetic drugs can cause fluid retention that can lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure and be managed accordingly. Dose reductions or discontinuation of the TZD should be considered in patients that progress to heart failure. The initiation of TZD therapy in patients with NYHA Class III or IV heart failure is contraindicated. Rosiglitazone contains an additional black box warning for the possibility of increased risk of myocardial ischemic events such as angina or myocardial infarction. This risk appeared higher in patients taking nitrates or insulin. Taking rosiglitazone with insulin or nitrates is not recommended.

Labeling for rosiglitazone/glimepiride (Avandaryl) and pioglitazone/glimepiride (Duetact) contains a warning for increased risk of cardiovascular mortality due to the sulfonylurea component.

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal dysfunction (serum creatinine $\geq$1.5 mg/dL for males and $\geq$1.4 mg/dL for females), acute or chronic metabolic acidosis, including diabetic ketoacidosis (with or without coma), pregnancy, or known hypersensitivity to metformin or other ingredients in the drug formulation.

Lactic acidosis is a rare, but potentially fatal, complication of metformin therapy. The risk is greater for patients experiencing sepsis, dehydration, hypoxemia, hypoperfusion, hepatic/renal impairment, or those who consume excess alcohol. Metformin should be used with caution in patients with renal insufficiency or patients undergoing radiologic procedures who need intravenous iodinated contrast agents.

Use of glimepiride, metformin, pioglitazone, or rosiglitazone is contraindicated in patients with known hypersensitivity to these products or any of their components.

Precautions[32,33,34,35,36,37]

For pioglitazone and rosiglitazone, liver function tests are recommended at the start of therapy, then periodically thereafter at the discretion of the physician. This recommendation extends to all products in combination with TZDs. If the alanine aminotransferase (ALT) rises, it should be monitored closely. If it exceeds 2.5 to three times the upper limit of normal, the drug should be discontinued.

Dose-related weight gain has been observed in patients taking pioglitazone and rosiglitazone either alone or in combination with other hypoglycemic agents.

Dose-related decreases in mean hemoglobin and hematocrit may occur in adults taking pioglitazone or rosiglitazone either alone or in combination with other hypoglycemic agents.

In premenopausal anovulatory women, the initiation of therapy with pioglitazone or rosiglitazone may cause ovulation; therefore, patients may be at an increased risk for pregnancy. Adequate contraception is recommended.

Do not use pioglitazone or rosiglitazone to treat type 1 diabetes or diabetic ketoacidosis.

Caution should be used with patients experiencing hypoxic states or undergoing surgical procedures and patients with hepatic impairment or with excessive alcohol intake. Due to the age-related decline of renal function, do not titrate metformin to the upper dosage range in elderly patients (>80 years of age) even for patients with serum creatinine levels within the normal range.

In PROactive, a randomized trial with type 2 diabetic patients, an increased incidence of bone fractures was noted in pioglitazone patients (5.1 percent versus 2.5 percent for patients taking placebo).[38] This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures were nonvertebral (lower and upper limb), and no increase was seen in men taking pioglitazone.

Based on a review of the safety data from the ADOPT study, rosiglitazone labeling includes mention of an increased number of arm, hand, and foot fractures among women taking rosiglitazone for newly diagnosed type 2 diabetes.[39] The fracture rate was 2.74 per 100 patient years for the 645 women treated with rosiglitazone versus 1.54 per 100 patient years for the 590 women in the metformin arm and 1.29 per 100 patient year for 605 women treated with glyburide. The increase in fractures was seen in the humerus, hand, and foot for women taking rosiglitazone; there was no increase in hip or spine fractures, usually associated with postmenopausal osteoporosis. Final results from ADOPT are due in 2009.

Macular edema has been reported in post-marketing experience in diabetic patients on TZD therapy. Some patients had improvement in their macular edema after discontinuation of TZD therapy. It is unknown whether or not there is a causal relationship between TZDs and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist, and should be promptly referred to an ophthalmologist if any kind of visual symptom is reported.

## *Drug Interactions*[40,41,42,43,44,45]

Pioglitazone (Actos) and rosiglitazone (Avandia) are predominantly metabolized by CYP2C8. If an inhibitor or inducer of CYP2C8 is started or stopped during treatment with either agent, changes in treatment may be needed based on clinical response. Additionally to a much lesser extent rosiglitazone is also metabolized by CYP2C9 and pioglitazone is metabolized by CYP3A4.

Exercise caution when using with drugs that are known to exacerbate hyperglycemia.

Cationic drugs such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin that are eliminated by renal tubular secretion have a theoretical potential interaction with metformin by competing for common renal tubular transport systems. No specific dosing changes are recommended. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine. No specific dosing changes are recommended.

## *Adverse Effects*

| Drug | Headache | Edema | Myalgia/ Fatigue | Anemia | Hyperglycemia | Diarrhea | Hypoglycemia |
|---|---|---|---|---|---|---|---|
| glimepiride (Amaryl)[46] n=746 | 1.5 | nr | nr | nr | nr | <1 | 0.9 to 1.7 |
| metformin (Glucophage)[47] n=141 | 5.7 (4.8) | nr | 1-5 | nr | nr | 53.2 (11.7) | 1 to 5 |
| pioglitazone (Actos)[48] n=606 | 9.1 (6.9) | 4.8 (1.2) | 5.4 (2.7) | ≤2 | 5.1 (8.1) | nr | nr |
| rosiglitazone (Avandia)[49] n=2,526 | 5.9 (5) | 4.8 (1.3) | 3.6 (5) | 1.9 (0.7) | 3.9 (5.7) | 2.3 (3.3) | 0.6 (0.2) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative. Incidences in parentheses are placebo. nr = not reported.

Adverse effects reported in the labeling for Actoplus Met, Avandaryl, Avandamet, and Duetact do not reflect the specific combination product.

Edema and CHF

The incidence of edema with the combination of pioglitazone and insulin was 15.3 percent and with insulin and placebo was seven percent. In a 16-week study, 1.1 percent of patients receiving insulin and pioglitazone developed heart failure, and no patients on insulin therapy alone developed heart failure.[50]

Combined and peripheral edema was reported more frequently in patients taking combination pioglitazone/metformin therapy (six percent) than metformin/placebo (2.5 percent).[51] Edema

 

was also higher in patients receiving rosiglitazone/metformin therapy (4.4 percent) than metformin/placebo (2.2 percent).

The incidence of edema with rosiglitazone in combination with insulin was 14.7 percent whereas insulin alone was 5.4 percent in a 26-week study.[52] New onset of heart failure was one percent with insulin, two percent with rosiglitazone 4 mg with insulin and three percent with rosiglitazone 8 mg with insulin.

Hypoglycemia

Hypoglycemia was reported more frequently in patients taking combination rosiglitazone/metformin therapy (three percent) than rosiglitazone (0.6 percent) or metformin (1.3 percent) monotherapy.[53]

Anemia

Anemia was also reported in a greater number of patients taking combination rosiglitazone/metformin therapy (7.1 percent) compared to rosiglitazone (1.9 percent) or metformin (2.2 percent) monotherapy. Anemia was reported in less than two percent of patients taking pioglitazone/metformin therapy.[54]

Effect on Cholesterol/Triglycerides

| Drug | Total-Cholesterol | HDL Cholesterol | LDL Cholesterol | Triglycerides |
|---|---|---|---|---|
| pioglitazone (Actos)[55] versus placebo | ↑ 6.4%*<br>↑ 4.4% | ↑ 19.1%<br>↑ 8.1% | ↑ 7.2%*<br>↑ 4.8% | ↓ 9.6%<br>↑ 4.8% |
| rosiglitazone (Avandia)[56] versus placebo | ↑ (percent increase not reported) | ↑ 14.2%<br>↑ 8% | ↑ 18.6%<br>↑ 4.8% | variable |

*not significantly different from placebo

## *Special Populations*[57,58,59,60,61,62]

*Pediatrics*

Although metformin is approved for use in children ages 10 and older, safety and effectiveness have not been established for pioglitazone (Actos) or rosiglitazone (Avandia) or their combinations with metformin in pediatric patients. Glimepiride also has not been studied in this population, nor has its combination with pioglitazone or rosiglitazone.

*Pregnancy*

All pioglitazone- and rosiglitazone- containing products are Pregnancy Category C.

*Ethnic groups*

A randomized, double-blind, placebo-controlled, parallel-group study was performed to determine the efficacy and tolerability of the addition of rosiglitazone to a regimen of glyburide once daily in African-American and Hispanic-American patients with type 2 diabetes previously inadequately controlled with at least two months of sulfonylurea monotherapy.[63] Patients were assigned to receive treatment with glyburide 10 or 20 mg daily plus rosiglitazone 8 mg or placebo daily for 24 weeks. The primary efficacy endpoint was the change from baseline in $HbA_1c$ after 24 weeks of treatment. A total of 245 patients (101 African-Americans, 144 Hispanic-Americans) were enrolled. In the overall study population, treatment with glyburide/rosiglitazone was associated with a significantly greater mean reduction from baseline in $HbA_1c$ compared with glyburide/placebo (between-group difference: -1.4 percent; $p<0.001$). When assessed by ethnicity, $HbA_1c$ values were significantly reduced with glyburide/rosiglitazone compared with glyburide/placebo in African-American patients and in Hispanic-American patients (both $p<0.001$). With glyburide/rosiglitazone, 17.6 percent of African-American patients and 25.8 percent of Hispanic-American patients achieved $HbA_1c$ <7 percent, compared with 4.5 and 1.4 percent of glyburide/placebo patients, respectively. The most frequently reported adverse events with glyburide/rosiglitazone were edema and weight increase.

### *Dosages*

| Drug | Initial dose | Maintenance dose | Availability |
|---|---|---|---|
| **TZDs** | | | |
| pioglitazone (Actos) | 15-30 mg daily | 15-45 mg daily | 15, 30, 45 mg tablets |
| - combination therapy | 15-30 mg daily | 15-30 mg daily | |
| rosiglitazone (Avandia) | 4 mg daily OR<br>2 mg twice daily | 2-4 mg twice daily OR<br>8 mg daily | 2, 4, 8 mg tablets |
| - combination therapy (sulfonylurea and/or metformin) | 4 mg daily OR<br>2 mg twice daily | 2-4 mg twice daily OR<br>8 mg daily | |
| **TZDs and glimepiride** | | | |
| pioglitazone/glimepiride (Duetact) | Prior therapy with glimepiride or pioglitazone:<br>30 mg/2 mg or 30 mg/4 mg once daily with the first meal of the day<br>Maximum daily dose: 45 mg/8 mg | | 30 mg/2 mg,<br>30 mg/4 mg tablets |
| rosiglitazone/glimepiride (Avandaryl) | 4 mg/1 mg once daily with the first meal of the day (consider 4 mg/2 mg if patient was on prior TZD or sulfonylurea therapy)<br>Maximum daily dose: 8 mg/4 mg | | 4 mg/1 mg,<br>4 mg/2 mg,<br>4 mg/4 mg,<br>8 mg/2 mg,<br>8 mg/4 mg tablets |
| **TZDs and metformin** | | | |
| pioglitazone/metformin (Actoplus Met) | Prior therapy with metformin:<br>15 mg/500 mg or<br>15 mg/850 mg once or twice daily | | 15 mg/500 mg,<br>15 mg/850 mg tablets |
| | Prior therapy with pioglitazone:<br>15 mg/850 mg once daily or 15 mg/500 mg twice daily | | |
| rosiglitazone/metformin (Avandamet) | Prior therapy with metformin 1,000 mg/day:<br>2 mg/500 mg twice daily<br>Prior therapy with metformin 2,000 mg/day:<br>2 mg/1,000 mg twice daily | | 2 mg/500 mg,<br>4 mg/500 mg,<br>2 mg/1,000 mg,<br>4 mg/1,000 mg tablets |
| | Prior therapy with rosiglitazone 4 mg/day:<br>2 mg/500 mg twice daily<br><br>Prior therapy with rosiglitazone 8 mg/day:<br>4 mg/500 mg twice daily | | |

Pioglitazone and rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with renal impairment.

Therapy with pioglitazone or rosiglitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT>2.5 times the upper limit of normal).

## *Clinical Trials*

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. In countries outside of the US, blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

No good quality comparative clinical trials of the combination products are available at this time.

pioglitazone (Actos) and insulin

In a 16-week, double-blind, multicenter study, 566 patients currently on a stable insulin regimen for at least 30 days who continued to have an $HbA_1c$ greater than eight percent were randomized to receive daily placebo or pioglitazone 15 mg or 30 mg.[64] At the end of treatment, patients receiving pioglitazone 15 mg or 30 mg had mean decreases in $HbA_1c$ (-1 and -1.3 percent, respectively; $p<0.0001$) and FPG (-34.5 and -48 mg/dL, respectively; $p<0.0001$) that were significantly lower than baseline and the placebo group. The 15 mg and 30 mg pioglitazone groups had significant increases in HDL-C, while the 30 mg group showed significant mean reductions in triglyceride levels compared to placebo. The incidences of weight increase, hypoglycemia, and edema were higher among patients receiving insulin plus pioglitazone.

pioglitazone (Actos), metformin (Glucophage), and insulin

In this multicenter, double-blind study, 222 patients with $HbA_1c$ >8 percent at screening were given titrated insulin therapy and then were randomly assigned to 20-week treatment with pioglitazone or placebo in combination with insulin, with or without concurrent metformin therapy.[65] More than 98 percent of patients were taking metformin prior to and during the study. Pioglitazone significantly reduced insulin dose requirements two weeks after treatment initiation ($p<0.05$). At the end of the study, pioglitazone reduced daily insulin dosages by 12 units ($p<0.001$). Relative to placebo, pioglitazone reduced daily insulin dosages by 12.7 units, while improving mean $HbA_1c$ levels (pioglitazone -1.6 versus placebo -1.4 percent; p=NS). More pioglitazone-treated patients experienced edema and weight gain than placebo patients.

 

pioglitazone (Actos), rosiglitazone (Avandia), and glimepiride (Amaryl)

A 12-month, multicenter, double-blind, randomized, controlled, parallel-group trial assessed 91 patients with type 2 diabetes and metabolic syndrome.[66] All patients had poor glycemic control or experienced one or more adverse effects with diet and oral hypoglycemic agents such as sulfonylureas or metformin. All patients received a fixed oral dose of glimepiride 4 mg/day for 12 months. Patients also were randomized to receive pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily for 12 months. Patients in both groups experienced significant increases in mean BMI at 12 months compared with baseline (4.92 and 6.17 percent, respectively; $p<0.05$). At 12 months, a 1.3 percent reduction in mean values for HbA1c ($p<0.01$) 19.3 percent in FPG ($p<0.01$), and 16.3 percent in postprandial plasma glucose ($p<0.01$) were observed; no significant differences were found between treatment groups. Although the glimepiride/pioglitazone group experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline, the glimepiride/rosiglitazone group experienced a significant increase in most lipid-related risk factors for cardiovascular disease. Of the 87 patients who completed the study, 6.7 percent of patients in the glimepiride/pioglitazone group and 11.9 percent of patients in the glimepiride/rosiglitazone group had transient, mild to moderate adverse events that did not cause withdrawal from the trial.

pioglitazone (Actos), rosiglitazone (Avandia), glimepiride (Amaryl), and metformin (Glucophage)

A randomized, double-blind, placebo-controlled, parallel-group, two-arm study enrolled 170 patients with type 2 diabetes.[67] Patients received glimepiride 2 mg (titrated to effect) or placebo in combination with an established regimen of immediate- or extended release metformin and rosiglitazone or pioglitazone for 26 weeks. The primary efficacy outcome was the change in $HbA_1c$ from baseline. $HbA_1c$ was significantly improved at endpoint with glimepiride combination therapy compared with placebo (-1.31 versus -0.33 percent, respectively; $p<0.001$). Of the patients who received glimepiride, 62.2 percent achieved an $HbA_1c$ value of <7 percent, compared with 26 percent of patients receiving placebo ($p<0.001$). At endpoint, the glimepiride combination significantly lowered FPG (-37.4 mg/dL; $p<0.001$), as well. Clinically significant adverse events, laboratory abnormalities, and rates of severe hypoglycemia were similar between treatment groups. The overall incidence of hypoglycemia, however, was 51.2 percent in the glimepiride group and 8.3 percent in the placebo group ($p<0.001$).

rosiglitazone (Avandia) and placebo

Three hundred and sixty-nine patients with type 2 diabetes were enrolled in a double-blind, parallel-group, placebo-controlled study.[68] Patients were randomly assigned to receive placebo or rosiglitazone at doses of 4, 8, or 12 mg daily. At eight weeks, FPG decreased significantly in the rosiglitazone 4 mg, 8 mg, and 12 mg groups (-0.9, -2.0 and -1.7 mmol/L; $p=0.0003$, $p<0.0001$, and $p<0.0001$, respectively) compared with placebo (+0.4 mmol/L). Improvements in FPG were seen for rosiglitazone 4 and 8 mg groups, but the 12 mg/day dose produced no additional improvement. The overall incidence of adverse events was similar in all treatment groups.

In a double-blind study, 959 patients were randomized to placebo or rosiglitazone 4 mg or 8 mg for 26 weeks. The primary measure of efficacy was change in the $HbA_1c$ concentration.[69] Rosiglitazone produced reductions in $HbA_1c$ of -0.8 to -1.5 percent compared with placebo. Approximately 33 percent of drug-naïve patients treated with rosiglitazone achieved $HbA_1c$ $\leq$7 percent at study end. The proportions of patients with at least one adverse event were

comparable among the rosiglitazone and placebo groups, with no evidence of hepatotoxicity in any treatment group.

After a four-week placebo run-in period, 493 patients with type 2 diabetes were randomized in a double-blind manner to receive rosiglitazone 2 mg or 4 mg or placebo twice daily for 26 weeks.[70] The primary end point was change in $HbA_1c$. Rosiglitazone 2 and 4 mg twice daily decreased mean $HbA_1c$ relative to placebo by -1.2 and -1.5 percentage points, respectively, and reduced FPG concentrations relative to placebo by -3.22 and -4.22 mmol/L, respectively. There was no increase in adverse events with rosiglitazone.

After a two-week placebo run-in phase, 303 patients with type 2 diabetes were randomly assigned in double-blind fashion to eight weeks of treatment with placebo or 2, 4, or 6 mg of rosiglitazone twice daily (FDA-approved maximum dose is 8 mg daily).[71] All rosiglitazone doses significantly reduced FPG compared with baseline and showed significantly reduced peak postprandial glucose concentrations compared with baseline ($p<0.001$) and with placebo ($p<0.0001$). Rosiglitazone 4 and 6 mg twice daily regimens prevented increases in $HbA_1c$ that were observed in the placebo group. The proportion of patients with one or more adverse event was similar in all four treatment groups with no evidence of hepatotoxicity.

rosiglitazone (Avandia), glyburide (Micronase®, Diabeta®), and metformin (Glucophage)

The efficacy and safety of adding rosiglitazone to an established regimen of glyburide/metformin in patients with type 2 diabetes who had not achieved adequate glycemic control ($HbA_1c$ between seven and ten percent) were evaluated.[72] Following an open-label, lead-in phase, 365 patients randomly received rosiglitazone 4 mg once daily or placebo in a double-blind manner. Based on glycemic response, rosiglitazone dose was maintained or increased to 4 mg twice daily. After 24 weeks, therapy with glyburide/metformin plus rosiglitazone resulted in a greater reduction (-1 percent, $p<0.001$) in $HbA_1c$ levels compared with combination therapy that included placebo (+0.1 percent). A larger proportion of patients (42 versus 14 percent) in the triple combination group attained $HbA_1c$ levels less than seven percent. The difference in FBG levels between groups was -48 mg/dL ($p<0.001$), favoring glyburide/metformin plus rosiglitazone. Adverse events of rosiglitazone reflected those reported in similar studies.

rosiglitazone (Avandia) and glipizide (Glucotrol)

A total of 227 patients with type 2 diabetes who were being treated with submaximal doses of sulfonylureas were randomized to receive rosiglitazone 4 mg or placebo daily in combination with glipizide 10 mg twice daily for two years in a double-blind, parallel-group study.[73] Rosiglitazone/glipizide significantly decreased $HbA_1c$, FPG, insulin resistance, plasma free fatty acids, and medical care utilization and improved treatment satisfaction compared with glipizide alone.

rosiglitazone (Avandia) and insulin

Three hundred nineteen type 2 diabetic patients with mean baseline $HbA_1c \geq 7.5$ percent and taking insulin twice daily were randomized in a double-blind manner to 26 weeks of additional treatment with rosiglitazone 4 or 8 mg daily or placebo.[74] Insulin dose could be decreased for safety reasons. The primary endpoint was reduction of $HbA_1c$ from baseline. By intent-to-treat analysis, treatment with rosiglitazone plus insulin resulted in a mean reduction from baseline in $HbA_1c$ of -1.2 percent ($p<0.0001$), with a 12 percent mean reduction of insulin dosage. Serious adverse events did not differ among groups.

 

rosiglitazone (Avandia) and metformin (Glucophage)

The efficacy of the combination of metformin and rosiglitazone compared to metformin alone was evaluated in 348 patients with type 2 diabetes who were inadequately controlled on metformin alone.[75] Patients were randomized in a double-blind fashion to metformin 2,500 mg daily plus placebo, metformin 2,500 mg plus rosiglitazone 4 mg daily, or metformin 2,500 mg daily plus rosiglitazone 8 mg daily for 26 weeks. $HbA_1c$, FPG, insulin sensitivity, and β-cell function improved significantly with the combination therapy in a dose-dependent manner. The mean $HbA_1c$ decrease was one percent in the rosiglitazone 4 mg group and 1.2 percent in the rosiglitazone 8 mg group. Twenty-eight percent of patients in the rosiglitazone 8 mg group achieved $HbA_1c$ less than seven percent. Dose-dependent increases in body weight and lipid profiles were observed. Adverse effects were similar in all groups.

The efficacy and safety of rosiglitazone 2 mg or 4 mg twice daily in combination with metformin 2,500 mg daily were evaluated in 116 patients whose type 2 diabetes was inadequately controlled with metformin alone.[76] The randomized, double-blind, placebo-controlled study was conducted for 26 weeks. Mean $HbA_1c$ levels decreased significantly from baseline to week 26 in the rosiglitazone 2 mg (-0.7 percent; p=0.0052) and 4 mg (-1.2 percent; p=0.0008) groups, but increased in the placebo group (+0.3 percent; p=0.2651). Mean FBG levels also improved significantly with metformin plus rosiglitazone therapy in a dose-dependent manner compared with placebo ($p \leq 0.0019$). The proportion of patients with one or more adverse events was similar across all three groups, with no cases of hepatotoxicity.

In a double-blind, randomized, parallel-group study, 766 subjects with a baseline metformin dose of 1,000 mg/day were randomized to receive either rosiglitazone 4 mg daily (4 mg/1000 mg) or an additional 500 mg/day of metformin.[77] Increases in the study medications to maximum doses were performed after eight weeks. After 24 weeks, rosiglitazone 8 mg/metformin 1,000 mg was at least as effective as 2,000 mg/day of metformin in improving $HbA_1c$ with mean reductions of -0.93 and -0.71 percent, respectively, from baseline in subjects that completed the study. In addition, a higher percentage of subjects in the rosiglitazone/metformin group achieved $HbA_1c$ <7 percent (58.1 versus 48.4 percent). The percentage of subjects experiencing a gastrointestinal side effect was 27.9 and 38.7 percent for the rosiglitazone/metformin and metformin groups, respectively.

### *Meta-Analyses*

pioglitazone (Actos)

To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events, a database containing individual patient-level time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.[78] The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. Data from a total of 19 trials, enrolling 16,390 patients, were combined by means of a fixed-effects model. Study drug treatment duration ranged from four months to 3.5 years. The primary outcome occurred in 375 of 8,554 patients (4.4 percent) receiving pioglitazone and 450 of 7,836 patients (5.7 percent) receiving control therapy (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.72-0.94; p=0.005). Individual components of the primary endpoint were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3 percent) of the pioglitazone (Actos)-treated patients and 139

(1.8 percent) of the control patients (HR, 1.41; 95% CI, 1.14-1.76; p=0.002). Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

pioglitazone (Actos) and rosiglitazone (Avandia)

A systematic review and meta-analysis of seven randomized, double-blind clinical trials of drug-related congestive heart failure in patients given TZDs (either rosiglitazone or pioglitazone) was performed.[79] The main outcome measures were development of congestive heart failure and the risk of cardiovascular death. Of the 20,191 patients, 360 who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). Results showed no heterogeneity of effects across studies, which indicated a class effect for TZDs. Compared with controls, patients given TZDs had increased risk for development of congestive heart failure across a wide background of cardiac risk (relative risk 1.72; p=0.002). By contrast, the risk of cardiovascular death was not increased with either of the two TZDs (0.93; p=0.68).

rosiglitazone (Avandia)

Published literature, the Food and Drug Administration website, and a clinical trials registry maintained by the drug manufacturer were searched for studies with the following criteria: study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes.[80] The inclusion criteria were met by 42 studies. All occurrences of myocardial infarction and death from cardiovascular causes were tabulated. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline $HbA_1c$ was approximately 8.2 percent. Compared to the control group, the odds ratio for the rosiglitazone group for myocardial infarction was 1.43 (95% CI, 1.03 to 1.98; p=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; p=0.06).

## *Summary*

As seen in the clinical trials, pioglitazone (Actos) and rosiglitazone (Avandia) are capable of lowering $HbA_1c$ by one to 1.5 percentage points when used as monotherapy in the treatment of type 2 diabetes. In combination with other agents used to lower blood glucose levels, including metformin and glimepiride, the level of $HbA_1c$ lowering is approximately an additional one percent.

In measuring the ability of pioglitazone and rosiglitazone to reduce other markers such as FPG, reductions of 40 to 60 mg/dL are possible with monotherapy, according to clinical trials. In combination with other antidiabetic agents, additional decreases of 35 to 50 mg/dL are seen.

Pioglitazone and rosiglitazone have similar efficacy as monotherapy and in combination with other agents. Despite both agents having beneficial effects on $HbA_1c$ and FPG, the 2009 ADA consensus algorithm does not recommend the use of rosiglitazone. Liver enzyme monitoring is required for both medications. Neither pioglitazone nor rosiglitazone products appear to have any advantage over each other in the treatment of special populations or the incidence of adverse reactions. Although the results of recent meta-analyses raise important questions, to draw conclusions from this method of evaluation would be premature.

 

The addition of combination products with metformin or glimepiride will allow more convenient administration for patients who require both drugs, but with added precautions for their use. Comparative data with these agents are not available at this time.

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