Drug Class Review: Thiazolidinediones

Generic Name	Brand Name	Manufacturer
Pioglitazone	Actos	Takeda Pharmaceuticals; Eli Lilly
Rosiglitazone	Avandia	GlaxoSmithKline

I. FDA Indications

Pioglitazone and rosiglitazone are indicated for monotherapy or for use in combination with a sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus.[1,2]

II. Pharmacology

Pioglitazone and rosiglitazone are thiazolidinediones (TZDs) that act primarily by decreasing insulin resistance. Their mechanism of action for improving insulin sensitivity is not yet fully understood. They are selective agonists for peroxisome proliferator-activated receptor-gamma (PPARγ). Activation of PPARγ receptors results in increased glucose transport into cells in adipose tissue, skeletal muscle, and liver.[1,2]

III. Pharmacokinetics

Pioglitazone and rosiglitazone are highly protein bound (>99%), primarily to serum albumin. Both are extensively metabolized in the liver through cytochrome P450 isoenzymes 2C8 (pioglitazone, rosiglitazone), 2C9 (rosiglitazone), and 3A4 (pioglitazone). Both have pharmacologically active metabolites. Pioglitazone is eliminated primarily in the feces, and rosiglitzone is eliminated primarily in the urine. The pharmacokinetics of pioglitazone and rosiglitazone are not influenced by age or ethnicity.[1,2]

IV. Clinical Efficacy

Monotherapy

Pioglitazone and rosiglitazone produced statistically significant improvements in fasting plasma glucose (FPG) and hemoglobin A1c (A1c) compared to baseline. Clinical studies showed that the mean absolute change in A1c from baseline ranged from 0% to -0.7% for rosiglitazone and +0.2% to –1.4% for pioglitazone. Limited data are published comparing rosiglitazone or pioglitazone monotherapy with other anti-diabetic monotherapy regimens. Based on the available data, the reduction in A1c level with rosiglitazone and pioglitazone appears to be less than that with sulfonylurea or metformin. However, these differences were not found to be statistically significant.[3-8] (Table 1)

Add-on therapy

When pioglitazone or rosiglitazone is added to another glycemic lowering agent in patients with type-2 diabetes not well controlled on monotherapy, both drugs produced a significantly greater reduction on A1c and FPG than continuing monotherapy with the other agent. These findings are consistent with other clinical studies that showed combination of glycemic lowering agents provides greater effect than using one alone.[2,9-13] (Table 2)

Other clinical outcomes studies

Due to the unique mechanism of action of TZDs, there are some data that showed these drugs may preserve pancreatic beta-cell function, and it has been suggested that they should therefore be used early in the disease process.[14,15] Troglitazone was the first TZDs introduced, but subsequently removed from the market due to rare cases of idiosyncratic hepatocellular injury leading to death or liver transplant during post-marketing clinical use. Prior to its removal from the market, in The Troglitazone in Prevention of Diabetes (TRIPOD) study, it was shown that treatment with troglitazone reduced endogenous insulin requirements, preserved beta-cell function and prevented type-2 diabetes in Hispanic women with prior gestational diabetes.[16,17] The Pioglitazone in Prevention of Diabetes (PIPOD) study is currently ongoing and testing whether the stability of glycemia and beta-cell function observed in subjects during TRIPOD can be maintained with pioglitazone. An interim report of this 4-year open-label study indicated that from 117 of 143 eligible women enrolled in PIPOD, 102 had their first annual oral glucose tolerance test after first year treatment with pioglitazone, 1 (1.3%) developed diabetes.

For 26 women who entered PIPOD with mild diabetes, 9 (35%) of them still had glucose levels in the diabetic range at the end of year 1. This interim report concludes that the protection from diabetes observed during TRIPOD persisted during the first year of pioglitazone treatment in PIPOD.[17]

Prevention of progressive islet beta-cell failure or long-term deterioration in glycemia is currently being investigated in clinical trials. A Diabetes Outcome Progression Trial (ADOPT) is a randomized, double-blind, multicenter study that evaluates the long term efficacy of monotherapy with rosiglitazone on glycemic control and on the progression of pathophysiological abnormalities associated with type-2 diabetes as compared with metformin or glyburide monotherapy in patients recently diagnosed with type-2 diabetes (<3 years).[18]

While sulfonylurea, metformin, and insulin products have been shown in clinical trials to reduce microvascular and macrovascular complications associated with diabetes, currently there are no data on long term effects on morbidity and mortality related to diabetes and cardiovascular disease for TZDs.[19] Long-term clinical outcomes studies are currently ongoing for pioglitazone and rosiglitazone.[20,21]

V. Adverse Effects

Generally, TZDs are well tolerated. The adverse effect profiles are similar between pioglitazone and rosiglitazone. With the exception of weight gain and peripheral edema, the incidence of adverse events with TZDs was similar to placebo in clinical trials. Common adverse events reported with TZDs were upper respiratory infection, injury, headache. As monotherapy, neither drug caused hypoglycemia, but in combination therapy, hypoglycemia risk is increased, and dose reduction in concomitant agent may be necessary.[1,2]

Dose-dependent weight gain of 0.7 kg to 5.3 kg has been reported in the clinical studies and seems to be a class effect. The larger mean increase was noted with add-on therapy with insulin while the least weight gain was seen when used in combination with metformin. The mechanism of weight gain with TZDs is unclear. It is likely multifactorial and may be related to fluid retention or fat accumulation. [1,2,22]

TZDs can cause fluid retention, which may exacerbate or lead to heart failure. The incidence of edema is about 3%-5% with TZDs monotherapy; however, when combined with insulin therapy, the incidence of edema can increase to 13%-16%, compared with 5%-7% in patients receiving insulin plus placebo. In clinical trials and post-marketing experience, combining pioglitazone or rosiglitazone with insulin resulted in the development of peripheral edema in approximately 16% of patients. Three of 10 patients who developed cardiac failure on rosiglitazone/insulin combination had no known prior evidence of heart failure, or pre-existing cardiac condition. In a clinical study comparing pioglitazone/insulin combination versus insulin monotherapy, four patients receiving the combination therapy developed heart failure compared to none receiving insulin monotherapy. All four cases had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. Patients with New York Heart Association (NYHA) Class III and IV heart failure were not included in clinical trials. Pioglitazone and rosiglitazone are not indicated in patients with NYHA Class III or IV heart failure. [1,2,22,23]

Pre-marketing and post-marketing clinical studies have shown that rosiglitazone and pioglitazone do not cause hepatoxicity any more than placebo or active comparators. However, the manufacturers of rosiglitazone and pioglitazone have recommended that liver function tests should be evaluated prior to the initiation of therapy in all patients, every two months for the first year of therapy, and then periodically thereafter. Furthermore, pioglitazone or rosiglitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or the alanine aminotransferase (ALT) levels exceed 2.5 times the upper limit of normal. If ALT levels exceeds 3 times the upper limit of normal or if the patient is jaundiced, pioglitazone or rosiglitazone therapy should be discontinued. [1,2,22]

Compared to other anti-diabetic agents, pioglitazone and rosiglitazone have shown different effects on lipid profile in clinical studies. For total and LDL levels, rosiglitazone caused significantly larger increase while pioglitazone produced no statistically significant differences compared with baseline and controls. Both TZDs caused a statistically significant increase from baseline in HDL levels. For triglyceride level, pioglitazone caused a statistically significant decrease from baseline and rosiglitazone produced no statistically significant differences. [22]

VI. Drug-Drug Interactions

Pioglitazone is metabolized by CYP2C8 and 3A4. Pharmacokinetic interaction studies have not been conducted with pioglitazone and other drugs metabolized by CYP3A4. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone. Patients receiving ketoconazole concomitantly with pioglitazone might need more frequent evaluation with respect to glycemic control. [1]

Rosiglitazone is primarily metabolized by CYP2C8, and to a lesser extent by 2C9. In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major CYP 450 enzymes at clinically relevant concentrations.[2]

VII. Pregnancy

Pregnancy Category C for both products. [1,2]

Therapy with TZDs may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone or rosiglitazone. [1,2]

VIII. Dosing

Pioglitazone is taken once daily without regard to meals. Dose can be initiated at 15 mg daily, and titrated up to 45 mg daily. [1]

Rosiglitazone is taken either as a single daily dose or divided dosing without regard to meals. The usual starting dose is 4 mg daily. The maximum recommended dose is 8 mg daily. [2]

Dose adjustment in patients with renal insufficiency is not recommended for pioglitazone or rosiglitazone. There are no data on the use of pioglitazone or rosiglitazone in patients under 18 years of age; therefore, use of these products in pediatric patients is not recommended. [1,2]

Pioglitazone is available in 15mg, 30mg, and 45mg tablets. [1]

Rosiglitazone is available in 2mg, 4mg, and 8mg tablets. [2]

VIX. Summary

The TZDs offers a unique mechanism of action for the management of type-2 diabetes by targeting insulin resistance. Current available clinical data suggests that they are effective in the treatment of type-2 diabetes as monotherapy or in combination with other anti-diabetic agents. However, evidence to show that the TZDs are superior to other anti-diabetic agents in glycemic control is lacking. Furthermore, long-term safety and effects on diabetes-related complication reduction are still pending at this time. More clinical data is warranted to better assess the role of TZDs in the management of type-2 diabetes.

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Table 1. Clinical studies: monotherapy

Study Design	Treatment Arms	Mean duration of diabetes / Mean baseline A1c / Prior Treatment	Efficacy (mean change from baseline at the end of the study)	
			A1c (%)	FPG (mg/dL)
Grunberger et al[3] RCT, DB, MC 26 weeks Type 2 diabetes N=959	RSG 4mg qd RSG 2mg bid RSG 8mg qd RSG 4mg bid PLB	5-6 years; 8.9%-9%; Diet/exercise or oral diabetes agent (agents not specified) - 25% drug-naïve - 60% monotherapy - 15% combination	RSG 4mg qd: 0* RSG 2mg bid: -0.1* RSG 8mg qd: -0.3* RSG 4mg bid:-0.7* PLB: +0.8 *p<0.0001 vs. PLB	RSG 4mg qd: -25 RSG 2mg bid: -35 RSG 8mg qd: -42 RSG 4mg bid: -55 PLB: +8 Significance not reported
Lebovitz et al[4] RCT, DB, MC 26 weeks Type 2 diabetes N=533	RSG 2mg bid RSG 4mg bid PLB	5 years; 8.8%-9%; Diet/exercise or oral diabetes agent (agents not specified) - 27% drug-naive - 66% monotherapy - 7% combination	RSG 2mg bid: -0.3* RSG 4mg bid: -0.6* PLB: +0.9 *p<0.0001 vs. PLB	RSG 2mg bid: -38* RSG 4mg bid: -54* PLB: +19 *p<0.0001 vs. PLB
Charbonnel et al[5] RCT, DB 52 weeks Type 2 diabetes N=587	RSG 2 mg bid RSG 4 mg bid GLB 2.5mg-15 mg qd (median titrated dose 7.5 mg qd)	Not reported; 8% Diet/exercise or oral diabetes agent (agents not specified) - 39% drug-naive - 51% monotherapy - 10% combination	RSG 2mg bid: -0.27 RSG 4mg bid: -0.53* GLB: -0.72 *Difference not statistically significant vs. GLB (p value not reported)	RSG 2mg bid: -25.4* RSG 4mg bid: -40.8** GLB: -30 *p=0.21 vs. GLB **p=0.033 vs. GLB
Aronoff et al[6] RCT, DB, MC 26 weeks Type 2 diabetes N=408	PIG 7.5 mg qd PIG 15 mg qd PIG 30mg qd PIG 45 mg qd PLB	Not reported; 10%; Diet/exercise or diabetes agent (agents not specified) - 31% drug-naive - 56% monotherapy - 13% combination	PIG 7.5 mg qd: +0.2 PIG 15 mg qd: -0.3* PIG 30 mg qd: -0.3* PIG 45 mg qd: -0.9* PLB: +0.7 *p≤0.05 vs. PLB	PIG 7.5 mg qd: -18.1* PIG 15 mg qd: -29.6* PIG 30 mg qd: -31.8* PIG 45 mg qd: -53.9* PLB: +9.4 *p≤0.05 vs. PLB
Schernthaner et al[7] RCT, MC 52 weeks Type 2 diabetes N=1199	PIG up to 45 mg qd MET up to 850 mg tid	Not reported; 8.6%; Diet/exercise	PIG: -1.42 MET: -1.5 Difference not statistically significant between groups (p value not reported)	PIG: -45 MET: -37.8 p=0.016 between groups
Pavo et al[8] RCT, DB, MC 32 weeks Type 2 diabetes N=205	PIG up to 45 mg qd (mean dose 41.5 mg qd) MET up to 850 mg tid (mean dose 2292 mg qd)	5-6 years; 8.6%; Not reported	PIG: -1.3* MET: -1.5 p=0.28 vs. MET	PIG: -54* MET: -50.4 p=0.628 vs. MET

RCT=randomized controlled trial, DB=double-blind, MC=multicenter, RSG=rosiglitazone, PIG=pioglitazone, MET=metformin, GLB=glyburide, FPG=fasting plasma glucose

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Table 2. Clinical studies: add-on therapy

Study Design	Treatment Arms	Mean duration of diabetes / Mean baseline A1c / Prior Treatment	Efficacy (mean change from baseline at the end of the study)	
			A1c (%)	FPG (mg/dL)
Fonseca et al[9] RCT, DB, MC 26 weeks Type 2 diabetes N=348	RSG 4 mg qd + MET 2.5 g qd RSG 8 mg qd + MET 2.5 g qd PLB + MET 2.5 g qd	7-8 years; 8.6%-8.9%; MET 2.5 g qd only x 4-7 weeks prior to randomization	RSG 4 /MET: -0.56* RSG 8/MET: -0.78* PLB/MET: +0.45 *p<0.001 vs. PLB/MET	RSG 4/MET: -32.4* RSG 8/MET: -48.6* PLB/MET: +5.94 *p<0.001 vs. PLB/MET
Product Information[2] RCT, DB 26 weeks Type 2 diabetes N=375	RSG 2 mg bid + SUL PLB + SUL	Not reported; 9.2%; SUL (specific agent or dose not reported)	RSG/SUL: -0.9* PLB/SUL: +0.2 *p≤0.0001 vs. PLB/SUL	RSG/SUL: -38* PLB/SUL: +6 *p≤0.0001 vs. PLB/SUL
Raskin et al[10] RCT, DB, MC 26 weeks Type 2 diabetes N=319	RSG 2 mg bid + INS RSG 4 mg bid + INS PLB + INS	11-12 years; 9%; Insulin bid (total daily dose ≥ 30 units) x 8 weeks prior to randomization	RSG 2/INS: -0.6* RSG 4/INS: -1.2* PLB/INS: +0.1 *p<0.0001 vs. PLB/INS	RSG 2/INS: -42* RSG 4/INS: -44* PLB/INS: +10.8 *p<0.0001 vs. PLB/INS
Kipnes et al[11] RCT, DB, MC 16 weeks Type 2 diabetes N=560	PIG 15 mg qd + SUL* PIG 30 mg qd + SUL* PLB + SUL* *SUL=GLB or GLP	Not reported; 10%; Sulfonylurea monotherapy x 2-4 weeks prior to randomization	PIG 15/SUL: -0.8* PIG/SUL: -1.2* PLB/SUL: +0.1 *p≤0.05 vs. PLB/SUL	PIG 15/SUL: -33.8* PIG 30/SUL: -52.3* PLB/SUL: +5.6 *p≤0.05 vs. PLB/SUL
Einhorn et al[12] RCT, DB, MC 16 weeks Type 2 diabetes N=328	PIG 30 mg qd + MET* PLB + MET* *dose not adjusted unless in response to hypoglycemia	Not reported; 9.8%; Metformin monotherapy x 4 weeks prior to randomization	PIG/MET: -0.64* PLB/MET: +0.19 *p≤0.05 vs. PLB/MET	PIG/MET: -42.8* PLB/MET: -5.2 *p≤0.05 vs. PLB/MET
Rosenstock et al[13] RCT, DB, MC 16 weeks Type 2 diabetes N=566	PIG 15 mg qd + INS PIG 30 mg qd + INS PLB + INS	Not reported; 9.8%; Insulin ≥30 units/day	PIG 15/INS: -0.99* PIG 30/INS: -1.26* PLB/INS: -0.26 *p≤0.05 vs. PLB/INS	PIG 15/INS: -34.5* PIG 30/INS: -48* PLB/INS: +0.6 *p≤0.05 vs. PLB/INS

RCT=randomized controlled trial, DB=double-blind, MC=multicenter, RSG=rosiglitazone, PIG=pioglitazone, MET=metformin, GLB=glyburide, GLP=glipizide, SUL=sulfonylurea, INS=insulin, FPG=fasting plasma glucose

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