Clinical and Economic Evaluation of Two Thiazolidinediones in the Management of Diabetes

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INTRODUCTION

According to the American Diabetes Association, more than 18 million people in the U.S. have diabetes. In the past 20 years, a number of advances in the management and treatment of diabetes have taken place. In contrast to earlier days, when insulin was the only available treatment, new classes of oral agents have been developed and introduced to the market over the years. These agents include the sulfonylureas (first-generation and second-generation), biguanides, alpha-glucosidase inhibitors, meglitinides, and thiazolidinediones (TZDs). The TZDs are of special interest because their mechanism of action involves a reduction in insulin resistance and because they improve some of the cardiovascular risk factors usually present in patients with type-2 (non–insulin-dependent, “adult-onset”) diabetes mellitus.

This review discusses the information needed to perform a comprehensive and systematic evaluation of two TZDs, rosiglitazone (Avandia®, GlaxoSmithKline) and pioglitazone (Actos®, Takeda). Both agents are indicated either as monotherapy or in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. Both agents may improve cardiovascular parameters, such as lipid levels, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic status. However, evidence is lacking regarding clinical outcomes such as vascular disease and mortality.

This article follows the structure of the Format for Formulary Submissions, as recommended by the Academy of Managed Care Pharmacy, to facilitate the formulary-selection process.

PRODUCT INFORMATION

The TZD class of antidiabetic agents, including rosiglitazone and pioglitazone, enhances glyceric control by improving insulin sensitivity in the peripheral tissues by selectively activating the peroxisome proliferator-activated receptor (PPAR)-gamma and by inhibiting hepatic gluconeogenesis. The TZDs are used in the management of type-2 diabetes mellitus and depend on the presence of insulin for their mechanism of action.

Pioglitazone is available as 15-, 30-, and 45-mg tablets; rosiglitazone is available as 2-, 4-, and 8-mg tablets. PPAR receptor-

PHARMACOKINETICS

Absorption

Both rosiglitazone and pioglitazone are well absorbed with excellent bioavailability. The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations of rosiglitazone are observed about one hour after dosing, whereas pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within two hours. Administration of both agents with food results in no clinically significant pharmacokinetic alterations.

The maximum plasma concentration (Cmax) and the area-under-the-curve (AUC) concentration of rosiglitazone and pioglitazone increase in a dose-proportional manner over the therapeutic dose range. Both drugs achieve a similar Cmax and show a linear increase in plasma drug concentration with elevated doses.

The time to peak concentration (Tmax) is another important parameter to consider. The more rapidly an orally administered agent can reach Cmax, the more closely its concentration curve will follow that of intravenous (IV) dosing. The absorption characteristics of these two agents appear to be similar.

Distribution

Protein-binding affinity is thought to be significant in establishing a drug’s volume of distribution (Vd). The Vd estimates the theoretical body space available for the distribution of a drug. A Vd greater than 1 liter/kg indicates penetration beyond the vasculature. Rosiglitazone, pioglitazone, and its active metabolites are extensively protein-bound (by more than 98%). The mean apparent volume of distribution (Vd/F) of pioglitazone following a single-dose administration is 0.63 ± 0.41 (mean ± SD) liters/kg of body weight.
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The mean oral steady-state volume of distribution (V\textsubscript{ss}/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. These differences may not translate into the clinical effectiveness of the agents.\textsuperscript{4,5}

Elimination\textsuperscript{4,5}

Following oral administration, rosiglitazone and pioglitazone are eliminated by both renal and nonrenal routes. Approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile, either unchanged or as metabolites, and is eliminated in the feces.

After oral or intravenous administration of carbon 14\textsuperscript{(14C)}-rosiglitazone maleate, approximately 64% of the dose is eliminated in the urine and 23% is eliminated in the feces. The elimination half-life of rosiglitazone is three to four hours and is independent of the dose. The plasma half-life of 14C-rosiglitazone material ranges from 103 to 158 hours. The mean serum half-life of pioglitazone ranges from 3 to 7 hours; for total pioglitazone, the range is 16 to 24 hours.

Pioglitazone has an apparent clearance (CL/F) that has been calculated to be 5 to 7 liters/hour. The mean C\textsubscript{max} and AUC values are increased by 20% to 60% in female patients. Because therapy should be tailored for each patient to achieve glycemic control, no dose adjustment is recommended based on sex alone.

Pioglitazone therapy should not be initiated if there is clinical evidence of active liver disease or if serum alanine transaminase (ALT) levels exceed 2.5 times the upper limit of normal.\textsuperscript{4,5}

Drug–Drug Interactions\textsuperscript{4,5}

Interactions with some drugs can reduce the agent’s intestinal absorption, thereby affecting efficacy. In \textit{vivo} drug–drug interaction studies have suggested that pioglitazone may be a weak inducer of the cytochrome P450 (CYP450) isoform 3A4 enzyme. CYP3A4 is common to the metabolism of many drugs, including some immunosuppressive agents. Consequently, there might be some potential interaction between pioglitazone and post-transplantation immunosuppressive drugs.

\textit{In vitro} drug metabolism studies suggest that rosiglitazone does not inhibit any of the major cytochrome P450 enzymes at clinically relevant concentrations. In \textit{vivo} data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8 and, to a lesser extent, CYP2C9. Coadministration of pioglitazone 45 mg once daily for 15 days, followed by a single 7.5-mg dose of midazolam syrup, resulted in a 26% reduction in the midazolam C\textsubscript{max} and AUC concentration. Administration of another TZD with an oral contraceptive containing ethinyl estradiol and norethindrone reduces the plasma concentrations of both hormones by approximately 30%, which can result in loss of contraception.

Therefore, additional caution regarding contraception should be exercised in patients receiving pioglitazone and an oral contraceptive. However, rosiglitazone 4 mg twice daily had no clinically relevant effect on the pharmacokinetics of ethinyl estradiol and norethindrone.\textsuperscript{4,5}

Drug–Food Interactions\textsuperscript{4,5}

The TZDs are not affected significantly by coadministration of food. Taking both agents with food results in no clinically significant pharmacokinetic alterations.\textsuperscript{4,5}

PHARMACODYNAMICS

In patients with type-2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower values of blood glucose, plasma insulin, and glycosylated hemoglobin (Hb\textsubscript{A\textsubscript{1c}}). Based on results from an open-label extension study, the glucose-lowering effects of pioglitazone appeared to persist for at least one year. In controlled clinical trials, pioglitazone, in combination with sulfonylurea, metformin, or insulin, had an additive effect on glycemic control. Patients with lipid abnormalities were included in clinical trials of pioglitazone.

Overall, patients receiving pioglitazone experienced mean decreases in triglycerides, mean increases in high-density lipoprotein-cholesterol (HDL-C), and no consistent changes in low-density lipoprotein-cholesterol (LDL-C) or total cholesterol (TC).\textsuperscript{5} However, in a double-blind, randomized study of piragliptone and placebo, pioglitazone decreased the LDL particle size in patients with normolipidemia and hypertension.\textsuperscript{6} It is worth mentioning that insulin resistance is causally related to hypertension, and a correlation exists between plasma insulin concentrations and blood pressure readings.\textsuperscript{9,10}

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels in patients receiving pioglitazone doses of 15, 30, and 45 mg, compared with a mean increase in triglycerides in the placebo patients. Mean HDL-C levels increased to a greater extent in patients receiving pioglitazone than in the placebo-treated patients. There were no consistent differences in LDL-C or TC levels with pioglitazone or with placebo.

At the steady state, two of the pharmacologically active metabolites of pioglitazone—metabolites III (m-III) and IV (M-IV)—reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in type-2 diabetic patients, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration time curve.\textsuperscript{5}

A study by Lebovitz et al.\textsuperscript{11} published in 2001, assessed the efficacy and safety of a monotherapy regimen of rosiglitazone in patients with type-2 diabetes. Compared with placebo, rosiglitazone 2 and 4 mg decreased mean Hb\textsubscript{A\textsubscript{1c}} levels by 1.2 and 1.5 percentage points, respectively, and reduced fasting plasma glucose concentrations by 3.22 and 4.22 mmol/L, respectively. Rosiglitazone, compared with placebo, also reduced albumin–creatinine ratios by approximately 30%, decreased levels of plasma free fatty acids, and increased plasma HDL-C and LDL-C. Other studies support the findings of Lebovitz et al. by re-emphasizing that rosiglitazone improves insulin sensitivity and lowers blood glucose in patients with type-2 diabetes.\textsuperscript{12–14}

In a randomized double-blind controlled trial in 36 outpatient
insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type-2 diabetes. They found that peripheral glucose uptake increased significantly with rosiglitazone but not with metformin. Rosiglitazone was associated with a reduction in hepatic fat and an increase in insulin clearance.

Rosiglitazone is not likely to cause hepatotoxicity, contrary to an idiosyncratic association of other TZDs, such as troglitazone (Rezulin®), with hepatic reactions leading to liver failure.25 (Warner-Lambert withdrew troglitazone from the market in 2000.) Indeed, in 13 double-blind studies, Lebovitz et al.26 assessed the association between three TZDs (troglitazone, pioglitazone, and rosiglitazone) and liver enzyme levels. They found that 1.91% of 2,510 patients receiving troglitazone, 0.26% of 1,526 patients treated with pioglitazone, and 0.17% of 3,503 patients treated with rosiglitazone had ALT levels that were more than three times the upper limits of the reference range.

Protein-binding affinity is also important in determining the amount of drug available for antidiabetic action. It is commonly accepted that only the unbound drug has activity; hence, the more highly bound the drug, the less free it is to exert its effect. Therefore, the extensive protein binding of the TZDs (above 98%)4,5 allows for very little of the unbound drug to be available, thus lowering the AUC concentration.

### PHARMACOKINETICS IN PATIENTS WITH TYPE-2 DIABETES

In population pharmacokinetic analyses from three large clinical trials, including 642 men and 405 women with type-2 diabetes (35 to 80 years of age), the pharmacokinetic properties of rosiglitazone were not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and the oral steady-state volume of distribution (Vss/F) rose with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F varied by less than 1.7-fold; that of Vss/F varied by less than 2.3-fold. Rosiglitazone’s CL/F was also influenced by both weight and sex, being lower by approximately 15% in women.

### SUPPORTING CLINICAL DATA: THE CASE FOR TZD THERAPY IN DIABETES

#### Efficacy and Spectrum of Action

TZDs are approved for the treatment of hyperglycemia in patients with type-2 diabetes, even though their effects have varied. According to placebo-controlled studies, both pioglitazone and rosiglitazone decrease HbA1c values by 1% to 1.5%.27 In some analyses, however, clinical chart reviews showed no significant differences in HbA1c reductions between the two agents.

Rosiglitazone seems to increase both TC and LDL-C concentrations. Pioglitazone decreases TC and triglycerides and increases HDL-C levels. They found that 1.91% of 2,510 patients receiving troglitazone, 0.26% of 1,526 patients treated with pioglitazone, and 0.17% of 3,503 patients treated with rosiglitazone had ALT levels that were more than three times the upper limits of the reference range.

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Tolerability

It is well accepted that TZDs may cause volume expansion and peripheral edema. The edema that sometimes accompanies the use of a TZD can be worrisome, because it may be a harbinger of congestive heart failure (CHF).31 There is a growing concern that the use of TZDs is associated with CHF;27 although this relationship is unclear. The American Heart Association and the American Diabetes Association have issued an official statement on the use of TZDs and have developed guidelines to minimize the risk of heart failure.

The possible association of TZDs with the risk of CHF has been documented in several studies, although no prospective controlled clinical trials have been completed.32,33 Tang et al., at the Cleveland Clinic,31 reported that despite the association of TZDs with an increased risk of edema, the additional risk of cardiovascular disease attributable to TZDs is relatively small. On the other hand, a published longitudinal observational study by Delea et al.34 reported that the initiation of TZDs was associated with an increased risk of incident CHF (hazard ratio 1.7; P < .001). If TZDs do confer an increased risk for CHF, one might expect a dose–response effect; however, no such evidence was reported in the Delea study.

Researchers are conducting a long-term study, funded by the American Diabetes Association, of TZD use and CHF in the Kaiser Permanente Northern California Diabetes Registry. Preliminary analyses have noted a substantially elevated prevalence of several markers of disease severity, including poor glycemic control (HbA1c above 9.5%), among patients initiating new diabetes medications compared with patients who were not starting new therapies. Moreover, compared with those initiating other therapies, the TZD initiators had more CHF risk factors, including the greatest prevalence of ischemic heart disease, hypertension, elevated urinary albumin excretion, elevated serum creatinine, microalbuminuria, and obesity; the poorest glycemic control; and the lowest mean HDL-C levels. These patients were also those most likely to need medications for dyslipidemia and hypertension, and they had the highest utilization of outpatient and inpatient services.

In an observational study by Masoudi et al.,35 the use of a TZD combined with metformin was not associated with increased mortality in older patients with diabetes and heart failure. The authors also noted that patients in their study sample might have better outcomes with the use of either TZDs or metformin.

Thus, TZDs were initiated more frequently in diabetic patients with more advanced disease. Because there are no generic TZDs at present, these expensive therapies will probably be reserved for more severe or advanced cases of diabetes.

IMPACT MODEL REPORT

Indications

Even though TZDs have been tested experimentally for other insulin-resistant conditions (e.g., non-alcoholic fatty liver disease, polycystic ovary syndrome, and lipodystrophies), these agents are indicated only for the treatment of type-2 diabetes at this time.47

Contraindications

TZDs are not intended for patients with clinical evidence of active liver disease. Rosiglitazone is contraindicated for patients with sensitivity to this product or any of its components.4 Pioglitazone is contraindicated for patients with diabetic ketoacidosis, hypersensitivity to pioglitazone products, or New York Heart Association class III or IV CHF.5

Cost and Economic Burden

Diabetes is the fifth leading cause of death by disease in the U.S., and it increases the risk of complications such as cardiovascular disease, blindness, kidney failure, extremity amputations, neurological disorders, and other chronic conditions.36 The death toll of patients with type-2 diabetes and its complications in the U.S. exceeds 500 people every day. Although type-2 diabetes can sometimes be treated with diet and exercise, many patients require the addition of an oral antidiabetic agent or a combination of these medications as part of their management program.

For individual countries, the direct health care costs of diabetes range from 2.5% to 15% of annual national health care budgets, depending on the prevalence of the disease in that country and the sophistication of the treatment available.37

In strictly financial terms, type-2 diabetes is one of the most costly health problems in the U.S., accounting for more than $40 billion in direct medical costs annually. The total cost of diabetes in the U.S. in 2002 was approximately $132 billion, including $91.8 billion in direct medical expenditures and $39.8 billion in indirect expenditures attributable to lost workdays, restricted activity days, mortality, and permanent disability.36

A study conducted in a 500-physician multispecialty medical group owned by a plan with 650,000 members showed that expenditures for diabetes medications and all drugs increased substantially within two health maintenance organizations (HMOs) and continue to represent a larger percentage of total expenditures for patients with diabetes.38 Nau et al. found that the increased use of multiple drugs for glycemic control, coupled with the increased use of lipid-modifying drugs and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, might have produced much of this increase.38

These findings are consistent with a study by Dubois et al.39 These investigators observed that although expenditures for diabetes drugs increased by more than 90% between 1994 and 1997, approximately 73% of this increase was a result of volume factors. However, the shift from low-cost sulfonylureas to more expensive drugs such as TZDs also contributed to the increased expenditures in these two HMOs. Nevertheless, there is evidence that the addition of rosiglitazone to sulfonylurea therapy might be associated with a decreased use of medical resources, notably hospitalization and emergency visits. This “add-on” approach, when compared with a monotherapeutic sulfonylurea regimen, has also been related to a decrease in disease-management costs.40

CONCLUSION

Overall, the TZD class of oral hypoglycemic agents presents a number of advantages, primarily (1) decreased insulin resistance, (2) improved glycemic control, (3) reduced triglyceride levels, and (4) elevated HDL-C levels.4,5 However, despite the major advantages of TZDs over the older therapies, TZDs sometimes present a number of undesirable but relatively minor side effects, such as water retention (which can
be associated with CHF), increased LDL-C levels, and weight gain. These adverse effects can add to the morbidity burden and may affect quality of life.

Even though TZDs present clinical advantages over other oral hypoglycemic medications, managed care plans will need to examine the cost-effectiveness of TZDs as it applies to their specific plan’s populations. As with other newer drugs, about which effectiveness data are limited, it is important that we accumulate such evidence from observational studies. Future directions in outcomes research will provide more information on the use of the TZDs and their risks and benefits in diverse populations, with their differing baseline risks and behavioral patterns.

REFERENCES


7. Ibid, p 129.


