Effectiveness of Rosiglitazone and Pioglitazone to Reduce Hemoglobin A_{1c} Levels in Veteran Patients With Type 2 Diabetes

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Reported drug efficacy can vary drastically when patients are treated in a real-world environment. These authors studied whether the treatment results from these medications are worth their safety risks.

When new therapeutic agents are introduced into the market, providers must weigh the risks against the benefits for each individual patient based on clinical trials (or efficacy) data. This evidence, while strong, is based on populations that may have limited resemblance to real patients. Additionally, as medications are used in practice, adverse reactions and adverse effects may become more apparent as larger numbers and different types of patients are treated. Effectiveness of medications in real-world practice settings should be analyzed to help providers make decisions on medication treatment.

With the introduction of thiazolidinediones (TZDs) for the treatment of type 2 diabetes mellitus, providers and health care organizations have had to consider the potential risks of using these agents vs their benefit of lowering an individual's blood glucose levels and potentially reducing microvascular complications of the disease. Controversy surrounds the use of TZDs in practice because of safety, efficacy, and effectiveness concerns.[1–9] When the effectiveness and safety of medications are called into question, it is important for practitioners to be able to make evidence-based decisions.

With regard to TZDs, there is a lack of effectiveness data to support the available efficacy information. Efficacy refers to whether the intervention can be successful when it is properly implemented under controlled conditions, whereas effectiveness refers to whether the intervention is typically successful in actual clinical practice. Efficacy is a necessary, but not a sufficient condition for effectiveness and is ideally established through randomized, controlled, experimental studies. Given the known safety concerns with TZDs, it is important to evaluate their effectiveness in an actual clinical setting to determine if the risk is worth the benefit. Therefore, we conducted a study among patients with type 2 diabetes at the New Mexico VA Health Care System (NMVAHCS) who had been prescribed 1 of the 2 TZDs currently FDA approved to treat type 2 diabetes.

The primary objective of our study was to evaluate the effectiveness of pioglitazone and rosiglitazone by measuring patients' change in hemoglobin A_{1c} (HbA_{1c}) levels after 6 months and 1 year of TZD therapy. The secondary objective was to evaluate the effectiveness data between rosiglitazone and pioglitazone in our patient population. Here, we discuss the efficacy data and safety concerns regarding rosiglitazone and pioglitazone and report our study results.

REPORTED EFFICACY AND SAFETY CONCERNS OF TZDs

The TZDs are a class of oral hypoglycemic drugs that increase insulin sensitivity as their primary effect. Both rosiglitazone and pioglitazone are indicated for monotherapy or for combined therapy with sulfonylureas (SUs), including repaglanide; metformin; or insulin. As indicated by the VHA Pharmacy Benefits Management/Medical Advisory Panel, TZDs, when used as monotherapy, lower HbA_{1c} levels an average of 0.2% to 0.7% from baseline and, as such, are rarely used as monotherapy.[9] The agents appear to be more efficacious when used in combination with other

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hypoglycemia medications with different mechanisms of action and generally are not chosen over metformin for initial therapy due to concerns about adverse effects, safety, and cost. The efficacy data have shown that both pioglitazone and rosiglitazone lower HbA_{1c} levels to the same extent,[9] and an average drop of 0.4% to 1.3% can be expected when either agent is combined with an SU, metformin, or insulin (Table 1). An adequate response to a TZD administered concomitantly with another agent typically is considered a drop in HbA_{1c} level of approximately 1%.[9]

Clinically relevant safety considerations associated with pioglitazone and rosiglitazone use include edema, heart failure, weight gain, and increase in alanine aminotransferase (ALT) levels with the potential to cause liver function abnormalities. Additional conflicting evidence exists with regard to the safety profile of rosiglitazone. Two recent meta-analyses of rosiglitazone have raised the possibility of additional cardiovascular risks, specifically myocardial infarction.[2,3] An interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study (a prospective trial to evaluate for cardiovascular outcomes) was inconclusive with regard to overall risk of hospitalizations or death from cardiovascular causes.[10] Most recently, however, during the course of the FDA's review of the RECORD study, questions arose about the potential bias in the identification of cardiovascular events. In response to data that suggest an elevated risk of cardiovascular events, such as myocardial infarcation or stroke, in patients treated with rosiglitazone, the FDA has announced that it will significantly restrict the use of rosiglitazone in patients with type 2 diabetes who cannot control their condition with other medications.[11]

Table 1. Average HbA_{1c} level decrease that can be achieved by combined TZD therapy[9]

Therapy	Average HbA_{1c} level decrease, %[a]
TZD and a sulfonylurea	0.5–1.2
TZD and metformin	0.6–0.8
TZD and insulin	0.4–1.3

HbA_{1c} = hemoglobin A_{1c}; TZD = thiazolidinedione. [a]Values are representative of efficacy data and not effectiveness data.

A meta-analysis of pioglitazone did not show the same effect on cardiovascular risks.[12] Given the recent information regarding increased risk of myocardial infarction with rosiglitazone use, although not conclusive, it has been suggested that rosiglitazone use should be curtailed[4,8–10,12] and that perhaps pioglitazone should be used in its place. It is important to mention that, in addition to the recent rosiglitazone safety concerns, the FDA is also reviewing data from an ongoing, 10-year epidemiologic study designed to evaluate whether piogolitazone is associated with an increased risk of bladder cancer. Findings from studies in animals and humans suggest this is a potential safety risk that needs further study.[13]

METHODS

This retrospective database analysis was undertaken using the computer systems and software of the NM-VAHCS Outcomes Research Program to query and gather data on patients prescribed TZDs on an outpatient basis. Using the computerized patient record system we identified all veteran patients, or eligible beneficiaries, receiving care at the Raymond G. Murphy VA Medical Center (VAMC) in Albuquerque, New Mexico, or at any of its corresponding community-based outpatient clinics (CBOCs), with a diagnosis of type 2 diabetes, as identified by *International Classification of Diseases, 9th Revision* (ICD-9) codes on the problem lists, and received rosiglitazone or pioglitazone between 1998 and 2007 for at least 365 days. The data were collected using deidentified patient codes. All patients with an HbA_{1c} test completed within 1 year prior to the start of TZD therapy and a repeat HbA_{1c} test completed at least 10 weeks after TZD initiation but no longer than 365 days after TZD initiation, were included in the analysis.

Study data were imported into commercial relational database software (Microsoft Office Access, Microsoft Corporation, Redmond, Washington) and analyzed to determine the difference from baseline in patients' HbA_{1c} levels after 6 months of TZD therapy and after 1 year of TZD therapy. The data were further analyzed to evaluate if there was a difference in the effectiveness of rosiglitazone vs pioglitazone.

Currently at the NMVAHCS, TZDs are not approved for patients who have any of the following conditions: type 1 diabetes, prediabetes (defined as an impaired fasting glucose level or impaired glucose tolerance test results), New York Heart Association class III or IV heart failure, evidence of active liver disease or an ALT level greater than 2.5 times the upper limit of normal, previously developed significant heart failure while taking another TZD, or jaundice while

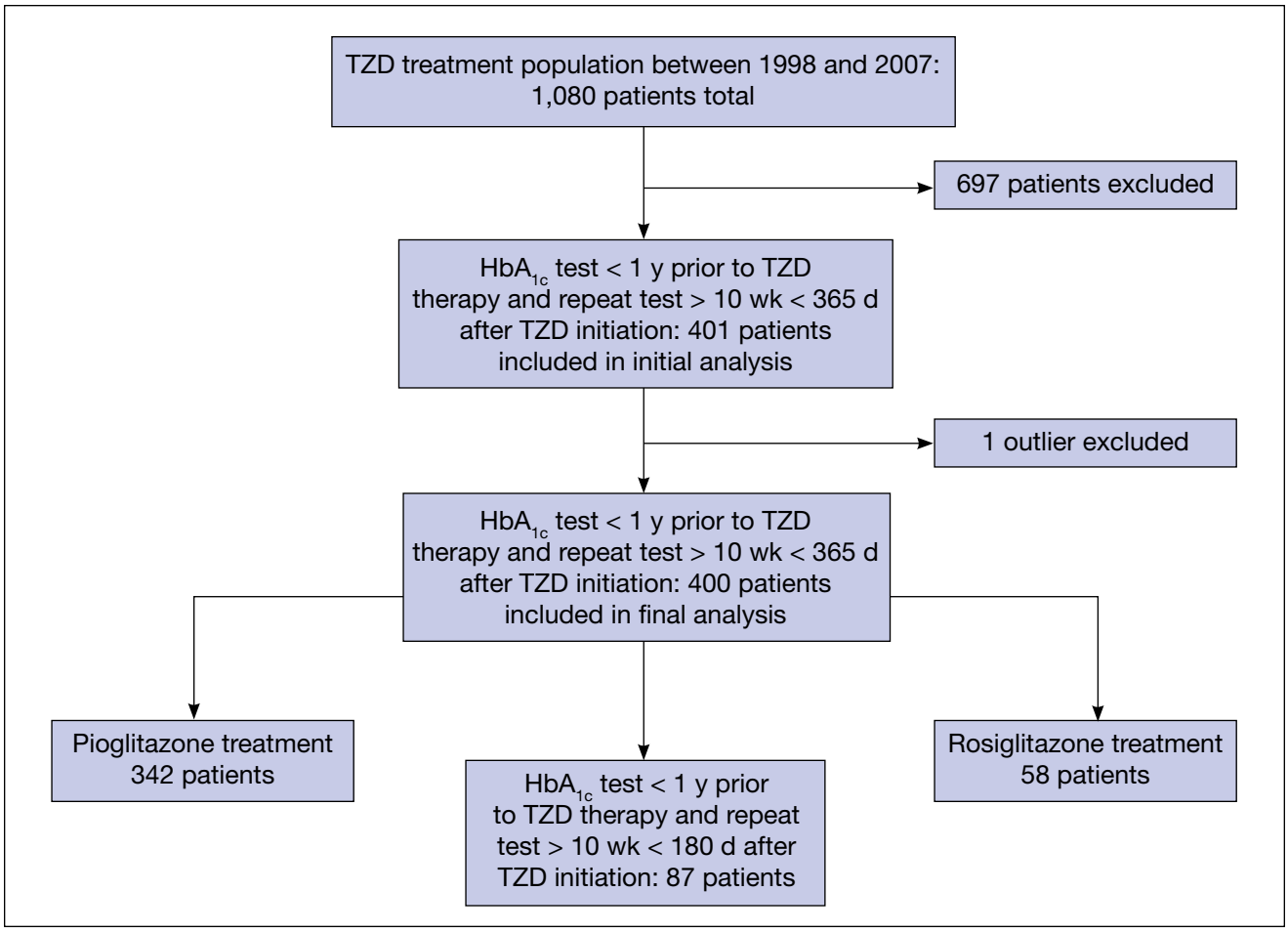

Figure. Study sample flowchart.

taking another TZD. Use of TZDs is currently restricted to NMVAHCS patients who have intolerance, contraindications, or inadequate glycemic control with SUs or metformin and are not suitable candidates for insulin therapy. Therefore, patients who began TZD therapy but received insulin therapy between HbA_{1c} level measurements during the study period were excluded from analysis, as insulin therapy could potentially have a significant impact on HbA_{1c} level reduction.

Additionally, because many veteran patients receive a 90-day supply of their medication rather than a 30-day supply, patients were excluded if they did not fill at least 91 days of TZD medication. This was done in an effort to eliminate those patients who had only 1 prescription filled because there was an adverse effect with the medication or the patient was nonadherent.

Patients were further excluded from the study if they did not have an HbA_{1c} level recorded in their medical record within 1 year prior to the start of TZD therapy and a repeat HbA_{1c} level recorded at least 10 weeks after TZD initiation but no longer than 365 days after TZD initiation. Although it would be optimal to check a patient's HbA_{1c} level 12 weeks after he or she began taking a TZD, we chose 10 weeks following TZD initiation to include those patients who may have had their HbA_{1c} test completed early. We felt that any HbA_{1c} test completed earlier than 10 weeks was too soon, and these patients were excluded. We also felt that any initial HbA_{1c} test completed outside 1 year of TZD initiation was too far out to include in the data pool. Although these time frames do not reflect ideal laboratory follow up after initiation of TZD treatment, they do reflect the reality of clinical practice and were used to include as many study patients as possible.

Study patients served as their own controls. Systat (Systat Software, Inc,

Table 2. Change in HbA_{1c} levels from baseline to 1 year in study patients taking rosiglitazone vs pioglitazone

Time point	Patients taking rosiglitazone (n = 58)	Patients taking pioglitazone (n = 342)	*P* value
Mean (SD) baseline HbA_{1c} level, %[a]	8.45 (1.71)	8.39 (1.56)	.57
Mean (SD) HbA_{1c} level at 1 y, %[b]	8.13 (1.62)	7.7 (1.5)	.054
Mean (SD) HbA_{1c} difference, %	0.32 (1.31)	0.6 (1.37)	.137

HbA_{1c} = hemoglobin A_{1c}. [a]HbA_{1c} test completed within 1 year prior to TZD initiation. [b]HbA_{1c} test completed within 1 year after TZD initiation.

Chicago, Illinois) was used to generate descriptive statistics, including the mean, standard deviation, and the largest individual HbA_{1c} level increases and decreases. Group differences in continuous variables were analyzed by the unpaired, 2-tailed *t* test.

The HbA_{1c} specimens were drawn either at the Raymond G. Murphy VAMC or at a corresponding CBOC, depending on where the patient received his or her primary care. All specimens were collected and analyzed at the Raymond G. Murphy VAMC central laboratory.

RESULTS

A total of 1,080 patients filled a prescription for either pioglitazone or rosiglitazone at the NMVAHCS for treatment of type 2 diabetes between 1998 and 2007. After excluding patients who did not meet inclusion criteria, the study population was limited to a total of 401 patients. One outlier was identified. This patient had an HbA_{1c} level reduction of 6 percentage points. As this result was greater than 2 standard deviations above the mean, a laboratory error was thought to be likely and this patient was removed from analysis. Final statistical analysis included a total number of 400 patients (Figure).

The mean (SD) decrease in HbA_{1c} level after 365 days of TZD therapy was 0.56% (1.36). The largest HbA_{1c} level decrease was 5.3 percentage points and the largest HbA_{1c} level increase was 3.3 percentage points. A total of 87 patients had an HbA_{1c} test completed between 10 weeks and 180 days after TZD initiation. Their HbA_{1c} levels decreased by a mean (SD) of 0.42% (1.2). The largest decrease in HbA_{1c} level was 2.2 percentage points and the largest increase in HbA_{1c} level was 3.3 percentage points.

Rosiglitazone vs pioglitazone

A total of 342 patients were treated with pioglitazone and 58 patients were treated with rosiglitazone. For patients taking pioglitazone, the mean (SD) decrease in HbA_{1c} level was 0.6% (1.37) (Table 2). The largest individual HbA_{1c} level decrease was 5.3 percentage points and the largest individual HbA_{1c} level increase was 3 percentage points. The mean length of therapy for patients treated with pioglitazone was 784 days (range, 91–2,628 days).

For the 58 patients taking rosiglitazone, the mean (SD) decrease in HbA_{1c} level was 0.32% (1.31). The mean (SD) length of therapy for patients treated with rosiglitazone was 527 days (range, 100–2,849 days).

There was no statistically significant difference between the effectiveness of rosiglitazone vs pioglitazone to reduce HbA_{1c} levels at 1-year follow up ($P = .54$).

DISCUSSION

This is a retrospective database analysis; therefore, cause and effect cannot be proven. However, it does supplement the findings from randomized trials on the effectiveness of TZD use in routine clinical practice. The major difficulty to overcome with estimation of true treatment effects (causal effects) from these data is the presence of confounding factors affecting both treatment and outcome. Patients who had TZD dosage changes, comorbidities, or were taking other medications that may have contributed to changes in HbA_{1c} levels were not excluded from this study. Additionally, patient lifestyle choices or population characteristics, such as age, gender, or race were not taken into account when analyzing and interpreting the results. It is important to emphasize that the majority of the patient population that receives care at the NMVAHCS are men. We did not evaluate adherence rates and differences in provider treatment patterns (for example, time of HbA_{1c} test completion after initiation of TZD); however, these results do reflect "real-world" variations of treatment. Despite the limitations of this study and considering that both TZDs were used as last-line therapy prior to initiation of insulin, it is important to note that the effectiveness results were comparable to the efficacy results as seen in controlled clinical trials.

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As compared with other oral glycemic agents currently available to treat type 2 diabetes, TZDs are a costly alternative. The large standard deviations found in this study suggest that individual responses varied considerably. Another trial looking at individual variations to TZD treatment may be warranted. Given the cost of TZDs, however, a periodic review of patients' responses to TZD treatment needs to be conducted to ensure their use is fiscally sound and to avoid potentially unnecessary adverse effects. As the mean decrease in HbA_{1c} level after 6 months of therapy corresponded to the mean decrease in HbA_{1c} level after 1 year of therapy, it appears reasonable that, if an adequate response is not seen within 6 months, medication discontinuation may be considered.

CONCLUSION

We found TZDs to be minimally effective among the study population at the NMVAHCS. Given the known safety concerns of these agents, providers should continue to ask themselves if the risk is worth the benefit on a case-by-case basis. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this column.

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