Association between Pioglitazone and Bladder Cancer in a Medicare population

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1. Background

The safety of pioglitazone (PIO) has been greatly debated in the literature over the past decade. PIO is a second-line oral glucose-lowering drug (GLD) first approved by the U.S. Food and Drug Administration (FDA) in 1999 as both as a monotherapy and to be used in combination with metformin, sulfonylurea, or insulin. After the first of the thiazolidinedione (TZD) class of drugs, troglitazone, was removed from the market shortly after its approval due to hepatotoxicity,[1] and the second, rosiglitazone, was issued an FDA black box warning in 2007 for myocardial infarction,[2,3] PIO use gained quick popularity due to its substantial effectiveness for reducing and maintaining blood glucose levels.[4-9] At its peak in 2008, 14.2 million PIO-containing prescriptions were dispensed in the US.[10] However, use drastically declined after the FDA issued a warning in 2011 that use greater than one year may be associated with an increased risk of bladder cancer.[11]

Preclinical carcinogenicity studies of PIO in male rats identified increased bladder tumors.[12] Although it was suspected that this was a rat-specific phenomenon that does not pose a urinary bladder cancer risk to humans, the FDA and the manufacturer agreed to a 10-year observational study to evaluate the potential risk of bladder cancer in humans. Since then, a variety of safety results have been published. Some demonstrating an increased risk of bladder cancer associated with any exposure to PIO[13,14], and for exposure after two[13,15] or five years.[16] Others identified no increased risk overall[15-22] or for exposure less than two years.[15,16,20] When stratified by sex, an increased risk was reported in men both overall[19] and for exposure after at least two years.[15]

2. Protocol Justification

A current methods study is in process to evaluate how results from use of the same data source, inclusion criteria and exposure can vary substantially based on the choice of cohort design (*incident versus prevalent exposure*), follow-up design (*intention-to-treat versus as-treated*) and referent group (*all non-users versus appropriate active comparators*). When the preliminary results comparing incident use of pioglitazone to incident use of dipeptidyl-peptidase 4 inhibitors (DPP) with an as-treated follow-up design were reviewed, we identified a preliminary signal of increased bladder cancer risk after two years of treatment. Although the 95% confidence interval of this estimate was inclusive of the null value of 1.0, the magnitude of the nearly two-fold point estimate (HR: 1.89 [95% CI: 0.97, 3.68]) motivated us to investigate further. Although bladder cancer represents only 4.5% of US cancers, it is the fourth most

common cancer in men.[23] Due to the importance of this public health safety concern, we have shifted our focus to do a full safety study and report results as soon as possible.

The 10-year observational study published in 2015 as a result of FDA and manufacturer agreement followed patients aged 40 years or older who entered the diabetic registry of Kaiser Permanente Northern California between 1997 and 2002 until 2012.[24] When compared to never use of PIO, ever use was not associated with bladder cancer risk after covariate adjustment (HR: 1.06 [95% CI, 0.89-1.26]). When stratified by duration of use <1.5, 1.5-4, and >4 years, the magnitude of the point estimates were close to 1.0 with 95% confidence intervals that included the null, but increased over time (0.88 [0.68-1.16], 1.03 [0.80-1.33], and 1.16 [0.87-1.54], respectively). A recent study published by Tuccori et al. using the United Kingdom Clinical Practice Research Datalink (CPRD) evaluated 14 years of data in patients newly treated with antidiabetic drugs between 2000 and 2013, with follow-up until 2014.[25] When compared to patients who were non-users of TZDs at time of PIO exposure, PIO use was associated with an increased risk of bladder cancer (1.63 [1.22-2.19]). When stratified by duration of use <=1, 1-2, and >2 years (1.33 [0.73-2.40], 1.66 [0.97-2.84], and 1.78 [1.21-2.64], respectively), risk increased over time.

Only two large observational studies assessing the association between PIO and bladder cancer have been published that use US cohorts.[21,24] These studies both used cohorts of commercially insured diabetic patients, including those aged less than 65. The first compared PIO to insulin[21], while the other included prevalent pioglitazone exposure and used a non-user comparison group.[24] The use of insulin injections may not be the best choice of active comparator for oral PIO, as it differs in route of administration (injection vs. oral), and is generally less expensive, and is more likely to be given to patients with more severe diabetes than PIO. When incident and prevalent users of a therapeutic agent are mixed within a cohort, harm may be under-estimated as the effect measure is weighted toward prevalent users who provide the majority of person-time and are less susceptible to the harm.[26,27] Bladder cancer occurs primarily in older people, with the average age at the time of diagnosis being 73 years old.[23] This study will employ an incident user, active comparator cohort design within a national representative sample of the US population over age 65, Medicare Part A, B and D claims data, to assess the association between PIO and bladder cancer, as compared to dipeptidyl-peptidase 4 inhibitors (DPP) and sulfonylureas.

3. Objectives

To examine the effect of initiation of Pioglitazone relative to DPP and/or sulfonylureas on the incidence of bladder cancer based on a new-user active comparator design. The specific comparisons are as follows:

i. *Pioglitazone vs. dipeptidyl-peptidase 4 inhibitors (Sitagliptin, Saxagliptin)*
ii. *Pioglitazone vs dipeptidyl-peptidase 4 inhibitors (Sitagliptin, Saxagliptin) OR Sulfonylureas (glyburide, glipizide, glimepiride).*
iii. *Pioglitazone vs. Sulfonylureas (glyburide, glipizide, glimepiride).*

4. Study Design

We will use an incident user, active comparator cohort design. Incident-user designs minimize the potential biases that that occur in prevalent user designs. [28-30] The use of an active comparator will help to balance the comparison groups. Specifically, the balance of diabetes severity in lieu of unavailable duration of diabetes.

5. Data source/Cohort Description:

Data will be abstracted from a 20% sample of Medicare Part A, B and D claims data from 2006-2013 (2014 data may be added if it becomes available). The cohort will include type II diabetic patients who initiated use of PIO, DPP, or sulfonylureas during the study period.

6. Exposure and Comparisons:

The analysis will be based on incident use of PIO and the active comparators [DPP (sitagliptin, saxagliptin) and/or sulfonylureas (glyburide, glipizide, glimepiride)] with at least two prescriptions claims within 90 days. The date of the first prescription claim will identify the date when a patient enters the cohort (cohort entry date) and the date of the second prescription claim will serve as start of follow-up (index date). Drug use will be defined using Anatomical Therapeutic Chemical (ATC; A10BG03: PIOGLITAZONE; A10BH: DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS; A10BB: SULFONAMIDES, UREA DERIVATIVES) classification codes, days supply, and fill dates from pharmacy claims from Medicare Part D.

7. Study Population/Inclusion criteria:

- Medicare enrollees at least 66 years of age
- Patients will be required to fill a 2nd prescription of the same drug class within (days supply + 90 days grace period) of the cohort entry date. This is to increase the probability that the new users are actually started on and taking the therapy. Follow-up will start from the date of the 2nd prescription fill (index date).
- Patients need to have at least 6 months of continuous Part D enrollment and at least 12 months of continuous enrollment in parts A and B prior to the cohort entry date.
- Since pharmacy data is available starting from 01 Jan 2007, the earliest cohort entry date will be 01 July 2007 (to ensure that the patients have at least 6 months of baseline pharmacy data).
- Prevalent users of a TZD in the 6 months prior to cohort entry date will be excluded (180-day wash-out period).
- Prevalent users of DPP in the 6 months prior to cohort entry date will be excluded (180-day wash-out period) from the PIO vs. DPP comparison.

- Prevalent users of sulfonylureas in the 6 months prior to cohort entry date will be excluded (180-day wash-out period) from the PIO vs. sulfonylureas comparison.
- Prevalent use of metformin will *not* be excluded from any of the analyses.
- Patients with a bladder cancer diagnoses in the period prior to and including the 2nd prescription claim (index date) will be excluded, in order to include only incident bladder cancer events.
- Patients who fulfill these inclusion criteria more than once will be enumerated and included as separate observations depending on their number.

8. Outcomes

The primary outcome of interest, bladder cancer, is defined as at ≥2 inpatient or outpatient diagnostic claims (ICD-9: 188.X non-in situ; 233.7 in situ) within 60 days, based on a validation study that showed higher positive predictive value (PPV) for diagnosis of cancers of the lung, colorectal, stomach, and breast, as well as lymphoma and leukemia using this method.(Setoguchi, Solomon et al. 2007).

9. Follow-up and analysis

In the primary 'as-treated' analysis, follow-up will start at the date of filling the 2nd prescription fill (index date) and will continue until the outcome occurs or until the first date of occurrence of death, end of study (31 Dec 2013 [2014 data may be added if it becomes available]), end of enrollment, or change in therapy (discontinuation, switch, or augment).

- ***Treatment discontinuation*** will be censored at no new prescription of a drug from the same drug class within (days supply + 90 days grace period) after the last prescription. Patients will be censored at days-supply + 90 days grace period.
- ***Switching*** will be censored at filling a prescription for a comparison drug without filling another prescription for the study drug within (days supply + 90 days grace period) after the last prescription. Patients will be censored at the date of filling the comparison drug. Switching to another drug from the same class or switching doses of the same drug will not be classified as switching.
- ***Augmenting*** will be defined as adding a prescription of a comparison drug with another prescription of the study drug within (days supply plus 90 days grace period). Patients will be censored at the date of filling the comparison drug. Patients will be censored at the date of filling the comparison drug.

In addition, 'intention to treat' (ITT) analyses are also planned where we will not censor for augmenting, switching or stopping. Therefore, follow-up will start at the date of filling the 2nd prescription fill (index date) and will continue until the outcome occurs or until the first date of occurrence of death, end of study (31 Dec 2013 [2014 data may be added if it becomes available]), or end of enrollment. Once a person meets the exposure definition, the person is considered

exposed from that point forward, even if they discontinue, switch, or augment.

Several additional analyses will be performed as sensitivity analyses (listed in section 11 below).

10. Covariates

Drug use will be measured in the 6 months (180 days) prior up to the cohort entry date. Co-morbidities will be measured in the 12 months (365 days) prior up to the cohort entry date. Analyses will be adjusted for potential confounding.

Demographics: age, gender, race/ethnicity, year of cohort entry date

Comorbidities: Any (yes/no) of the following diagnoses in the period prior to the cohort entry date:

Urinary Complications*: UTIs, BLADDER STONES, KIDNEY STONES

Diabetic Complications: NEPHROPATHY, NEUROPATHY, RETINOPATHY

Other Comorbidities: CONGESTIVE HEART FAILURE, CHRONIC KIDNEY DISEASE, CONNECTIVE TISSUE DISEASE, SMOKING STATUS (COPD), DEPRESSION, GI CONDITIONS, INFECTIONS (other - non UTI), MYOCARDIAL INFARCTION, STROKE

Co-Medications: Prescription filled (yes/no) in the period prior to the cohort entry date:

Diabetic Medications: INSULIN, METFORMIN, SULFONYLUREAS, SA Insulin, LA Insulin

Other Medications: ACEI, ANTICHOL, ARB, B2AGONISTS, BAS, BB, CAI, CCB, ESTROGEN, FIBRATE, GLYCOSIDE, LOOP, NIACIN, NONLOOP, OCP, PROGESTIN, STATINS, TESTO, THEO

Health System Use: Any of the following in the period prior to the cohort entry date:

Screening: Mammographies, Pap Smears, PSA Tests, Colonoscopies or Sigmoidoscopies

Other Health System Exposure: Office Visits, Flu Shots, Lipid Assessments, ECGs, Fecal Occult Blood Tests, ED Visits, Hospital Admissions, Long Stay Hospital Admission, Short Stay Hospital Admission, Skilled Nursing Facility Admissions

11. Sensitivity analyses

i. Primary outcome definition ($\geq$2 inpatient or outpatient bladder cancer claims within 60 days) will further be combined with an addition requirement of a Current Procedure Terminology (CPT-4) procedure claim for a bladder-cancer treatment within 3 months of the initial diagnosis to increase specificity. Treatment will be allowed to occur on the same day as the second bladder cancer diagnosis claim but has to occur after the first bladder cancer claim.

ii. Use of a 12-month induction period (exclusion of time from the beginning of follow-up to reduce the potential for spurious associations attributable to increased medicalization and screening after start of a new therapy and reduces the chances of protopathic bias that may occur if preclinical symptoms

of bladder cancer influence treatment choice) and a 6-month latency period (addition of time to the end of follow-up to allow for the longer latency between exposure and development of solid tumors).

iii. Shortening the 90-day grace period used to define change in treatment to 45 days and also extending to 180 days.

iv. Evaluate exposure looking at cumulative duration of PIO.

v. Exclusion of *any* cancer diagnosis except non-melanoma skin cancer in addition to the exclusion of bladder cancer in the period prior to and including the index date, as prevalent cancer may also affect the outcome.

References

1. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005;294:2581-6.
2. MedWatch Safety Alerts for Human Medical Products: 2007 Safety Alerts for Human Medical Products. 2007. (Accessed September 10, 2013, at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm.)
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
4. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifiro G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. Br J Clin Pharmacol 2013;75:861-8.
5. Hall GC, Smith HT, Curtis B, McMahon AD. Changes and predictors for change to thiazolidinedione prescribing in UK primary care following the rosiglitazone safety warning. Int J Clin Pract 2011;65:586-91.
6. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. Drug Saf 2012;35:471-80.
7. Stewart KA, Natzke B, Williams T, Granger E, Casscells SW, Croghan TW. Temporal trends in anti-diabetes drug use in TRICARE following safety warnings in 2007 about rosiglitazone. Pharmacoepidemiol Drug Saf 2009;18:1048-52.
8. George J, Hannah St, Lang CC. Thiazolidinediones and the influence of media adverse reporting on prescribing attitudes in practice (TZD-IMPACT) study. Cardiovasc Ther 2009;27:83-8.
9. Shah BR, Juurlink DN, Austin PC, Mamdani MM. New use of rosiglitazone decreased following publication of a meta-analysis suggesting harm. Diabet Med 2008;25:871-4.
10. Hampp C, Borders-Hemphill V, Moeny D, Wysowski D. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care 2014;37:1367-74.
11. Federal Drug Administration. Actos (pioglitazone): Ongoing Safety Review - Potential Increased Risk of Bladder Cancer. MedWatch Safety Alerts for Human Medical Products: 2011 Safety Alerts for Human Medical Products2011.
12. Suzuki S, Arnold LL, Pennington KL, et al. Effects of pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, on the urine and urothelium of the rat. Toxicol Sci 2010;113:349-57.
13. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. Bmj 2012;344:e3645.
14. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 2011;34:1369-71.
15. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 2011;34:916-22.
16. Mamtani R, Haynes K, Bilker WB, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. Journal of the National Cancer Institute 2012;104:1411-21.
17. Fujimoto K, Hamamoto Y, Honjo S, et al. Possible link of pioglitazone with bladder cancer in Japanese patients with type 2 diabetes. Diabetes research and clinical practice 2013;99:e21-3.
18. Kuo HW, Tiao MM, Ho SC, Yang CY. Pioglitazone use and the risk of bladder cancer. The Kaohsiung journal of medical sciences 2014;30:94-7.
19. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia 2012;55:1953-62.
20. Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. Diabetes Care 2012;35:278-80.
21. Vallarino C, Perez A, Fusco G, et al. Comparing pioglitazone to insulin with respect to cancer, cardiovascular and bone fracture endpoints, using propensity score weights. Clinical drug investigation 2013;33:621-31.
22. Wei L, MacDonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. Br J Clin Pharmacol 2013;75:254-9.
23. American Cancer Society. Bladder Cancer: Detailed Guide2014 Last Medical Review: 2/26/2014.
24. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. JAMA 2015;314:265-77. doi: 10.1001/jama.2015.7996.
25. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ 2016;352:i1541.:10.1136/bmj.i541.
26. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol 1994;47:731-7.
27. Cox E, Martin B, Van Staa T, Garbe E, Siebert U, Johnson M. Good research practices for comparative effectiveness research: Approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force—Part II. Value Health 2009;12:1053–61.
28. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20.

29. Johnson ES, Bartman BA, Briesacher BA, et al. The Incident User Design in Comparative Effectiveness Research. Effective Health Care Program Research Report No. 32. (Prepared under Contract No. HHSA290200500161). AHRQ Publication No. 11(12)-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
30. Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Pharmacoepidemiol Drug Saf 2013;22:1-6.