Global Versus Indian Perspective of Pioglitazone-induced Adverse Drug Reactions Including Bladder Cancer: A Comparative Retrospective Pharmacovigilance Analysis

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ABSTRACT

Purpose: In 2011, France and Germany banned pioglitazone due to a concomitant risk for bladder cancer. There has been continued debate about this topic. Therefore, we present a detailed analysis of data from individual case safety reports of pioglitazone use (PG-ICSRs) associated with bladder cancer reported worldwide and in India.

Methods: Data from PG-ICSRs reported by the National Coordination Centre's Pharmacovigilance Programme of India, as well as over 131 World Health Organization member countries in the Uppsala Monitoring Centre's VigiLyze pharmacovigilance database system, from January 1, 1967, to March 4, 2018, were collected. Comparisons between data from global and Indian PG-ICSRs were made by applying filters such as *country, bladder cancer, age group, gender, time period, information component,* and *data mining*.

Findings: Among the adverse drug reactions (ADRs) reported with pioglitazone use worldwide, *bladder cancer* and related terms were the most highly reported (43%). The most frequently co-reported concurrently used drug was metformin, which was included in 25% and 40% of overall and bladder cancer–specific PG-ICSRs, respectively. Suspected bladder cancer–specific pioglitazone-related reactions were reported in 27 countries, with 8548 serious and 1858 fatal cases and an information components value of 9.15. The Americas had the highest relative percentage of suspected bladder cancer in PG-ICSRs (53%), while the prevalence was much lower in India (2%). In both cohorts, men over the age of 45 years constituted the most highly reported population.

Implications: India has a very low prevalence of reported overall and bladder cancer–specific pioglitazone-related ADRs compared to Europe and the Americas. Possible explanations for the difference in reporting rates include variance in genetic makeup, low BC risk factor, pioglitazone prescription at a lower therapeutic dose, greater use of chemopreventive spices in the diet, higher frequency of metformin as a concurrent drug, and under-reporting of ADRs. (*Clin Ther*. 2019;41:2252–2262)

Keywords: adverse drug reactions, bladder cancer, Pharmacovigilance Programme of India, pioglitazone.

INTRODUCTION

Bladder cancer is the fourth most commonly reported cancer in men globally, and its prevalence has risen worldwide in the past decade. In India, since 1990, the incidence of bladder cancer–related mortality per 100,000 people has increased by 32.9%. The incidence of bladder cancer–related mortality in India is 0.8 per 100,000 people per year, which is ninefold and fourfold less than in Europe and America, respectively. In both men and women in India, bladder cancer–related deaths were most common in the subgroup over the age of 80 years; this cancer was least deadly in women aged 30–34 years and in men aged of 25–29 years. The overall rate of bladder cancer–related mortality in men is

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significantly higher than in women. Bladder cancer occurs mainly in older people, with approximately 9 of 10 cases occurring in individuals over the age of 45 years. White people have a twofold higher risk for developing bladder cancer compared with the Asian, African, and Native American populations.[1] The reasons for these differences are an area of active research. Several risk factors, such as smoking habit, race, age, gender, ethnicity, arsenic, low fluid intake, chronic bladder irritation and infections, family history, and long-term use of certain medicines such as pioglitazone, have been linked with an increased risk for bladder cancer.[2]

Pioglitazone lowers blood glucose levels and is used for treating diabetes mellitus (DM) type 2, either alone or in combination with a sulfonylurea, metformin, or insulin. Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator–activated receptor γ,[3] modulating the transcription of genes involved in the control of glucose and lipid metabolism.[4] Moreover, pioglitazone has been associated with a lower risk for cardiac adverse effects than has rosiglitazone, and research suggests that pioglitazone may be useful for treating major depression and autism, as it is thought to reduce glial cell activity and autoimmune/inflammation. Pioglitazone, the most frequently prescribed antidiabetic drug, remains banned in European countries such as France and Germany because of the identified associated risk for bladder cancer. The pioglitazone ban was based on an interim report by Lewis et al[5] from a cohort study that suggested a link between bladder cancer and pioglitazone therapy in DM. However, US health insurer Kaiser Permanente and a large study from the United Kingdom have thus far not confirmed an association between pioglitazone and bladder cancer. In 2016, pioglitazone was the 116th most prescribed medication in the United States, with >6 million prescriptions.

The US Food and Drug Administration (FDA) and the Indian drug regulatory body, the Central Drugs Standards Control Organization (CDSCO), have not banned pioglitazone from the market, but have advised patient counseling and the inclusion of a warning about bladder cancer risk in the drug's labeling. This information cautions patients about the risk for bladder cancer with the use of pioglitazone. The warnings state that patients with active bladder cancer or a history of bladder cancer, and those with noninvestigated hematuria, should not receive pioglitazone. Before using pioglitazone, individuals should be assessed for known risk factors for bladder cancer, including age, smoking history, exposure to occupational carcinogens or chemotherapy agents, or previous irradiation of the pelvic region. The benefit–risk of profile of pioglitazone continues to be debated, thus making continued monitoring of adverse drug reactions (ADRs) an essential component for improving health care and patient safety. The impact of ADRs in terms of morbidity, mortality, and economics is massive.[6] The spectrum of ADRs is very broad, ranging from general to life-threatening. ADRs are a not-so-silent menace to the health of a nation, heavily affecting governments' regulatory and financial policies. For a country such as India, with a population of about 1.3 billion people and a surfeit of novel drugs flooding the market, the reporting of ADRs should be on a war footing. India launched its own Pharmacovigilance Programme, with the mission of safeguarding public health, under the Ministry of Health and Family Welfare, Government of India, where the Indian Pharmacopoeia Commission is working as the National Coordination Center for Pharmacovigilance Programme of India (NCC-PvPI).[7] To monitor ADRs in India, at present, 270 ADR-monitoring centers are working under the NCC-PvPI. These ADR-monitoring centers are medical colleges and hospitals or public health programs, district hospitals, or corporate hospitals that collate, analyze, and submit ADRs to the NCC. The information collected at the NCC is transferred to the database, wherein it is analyzed further and then finally sent to the World Health Organization's Uppsala Monitoring Centre (WHO-UMC).

WHO defines *pharmacovigilance* as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. The purpose of pharmacovigilance is to enhance patient care and safety with respect to the use of medicines and to support public health programs by providing reliable information and effective assessment of the risk–benefit profiles of drugs. Pharmacovigilance or postmarketing surveillance of drugs relies on information gathered in the form of individual case tolerability reports (ICSRs), which provide a platform for obtaining essential scientific information for regulatory intervention. The pharmacovigilance-related

data are analyzed on the basis of scientific and clinical expertise, informing recommendations for a number of advisories such as drug alerts.[8,9] With this preface, here we report for the first time a comparative analysis of pioglitazone-related ADRs recorded in the VigiLyze pharmacovigilance database system of WHO-UMC. The present retrospective study analyzed in detail the experience with bladder cancer–specific pioglitazone-associated ADRs reported worldwide versus in India, with respect to geographic location, time, sex, age, co-reported reactions, use of concurrent drugs, and other statistical/quality parameters from ICSRs. All of these analyses will help in the evaluation of the risk–benefit profile of bladder cancer–specific pioglitazone-associated ADRs both globally and in India.

MATERIALS AND METHODS

All of the ICSRs reported from January 1, 1967, to March 4, 2018, in the WHO-UMC pharmacovigilance database system VigiLyze were analyzed. However, the India pharmacovigilance database in VigiLyze was initially incorporated from the year 1998, while the first ICSRs of pioglitazone were received worldwide and from India in 2000 and 2011, respectively. VigiLyze provides access to >16 million ICSRs in VigiBase, a global database of ICSRs submitted by over 131 WHO member countries, including India. The ICSRs of pioglitazone (PG-ICSR) reported by the NCC-PvPI as well as other WHO member countries in VigiLyze were analyzed in detail. VigiLyze provides a global, regional, or national outlook of suspected ADRs and is particularly valuable in cases of limited national data because it allows for comparisons between the global and national pharmacovigilance information available for that particular drug. During the current analysis of pioglitazone ADRs, several filters were applied in VigiLyze, including *country, bladder cancer, age group, sex, tenure, information component,* and *data mining*.

RESULTS

Geographic Distribution of PG-ICSRs

There were 16.9 million total ICSRs of drugs reported in VigiLyze from January 1, 1967, to March 4, 2018. Worldwide, 19,904 ICSRs were related to pioglitazone, of which the Americas had the highest (78%) prevalence, and the African continent, the lowest (0.1%), with India accounting for 159 ICSRs (0.8%) (Figure 1A). Among all of the reported PG-ICSRs across the world, 8622 (43%) were linked with *bladder cancer* and other similar terms. Similar to the distribution of overall PG-ICSRs, the geographic distribution of suspected bladder-cancer–specific ICSRs reported with pioglitazone use was highest in the Americas, with 8158 (95%), and lowest in India, with 3 (0.03%) (Figure 1A). In India, there were a total of 10 ICSRs with bladder cancer reported with all drugs, of which 3 were associated with pioglitazone use and 2 each with ciclosporin and prednisolone use. The relative percentages of overall and bladder cancer–specific PGICSRs (ie, the expected percentage of PG-ICSRs in the respective specific geographic region), were found to be highest in the Americas (8158/15,512 * 100 = 53%) and lowest in India (3/159 * 100 = 2%) (Figure 1B).

Allocation of PG-ICSRs by Year

Worldwide, there was a total of 19,904 PG-ICSRs between January 1, 1967, and March 4, 2018, with the highest number of cases reported in the year 2015 (5292 ICSRs, 27%) and the lowest in the year 2007 (67 ICSRs, 0.3%) (Figure 1C). Similarly, the prevalence of bladder cancer–specific PG-ICSRs was significantly higher in the year 2015 (4189 of 8622 ICSRs, 48.5%) compared to other years (Figure 1C). Worldwide, the first report of suspected bladder cancer–specific PG-ICSR was reported in 2004, and 101 ICSRs (1.17%) out of a total of 8622 ICSRs reported on or before December 31, 2011, in the database system. In India, however, the first report of bladder cancer–specific PG-ICSR was not reported until 2015, and as of now, 3 such cases have been reported of a total of 159 PG-ICSRs in India's database system (Figure 1D).

Patterns of PG-ICSRs in Men and Women

Worldwide, the distribution of overall PG-ICSRs was reasonably higher in men (37%) compared to women (30%), while there was an intermediate percentage of PG-ICSRs (34%) in which the sex of the patient was unknown (Figure 2A). The percentage of PG-ICSRs associated with bladder cancer was fivefold higher in the male population (27%) in comparison to the female population (6%). In 67% of PG-ICSRs with bladder cancer, the sex of the patient was not mentioned (Figure 2A). In the Indian cohort, of 159 PGICSRs, 3 were specific for

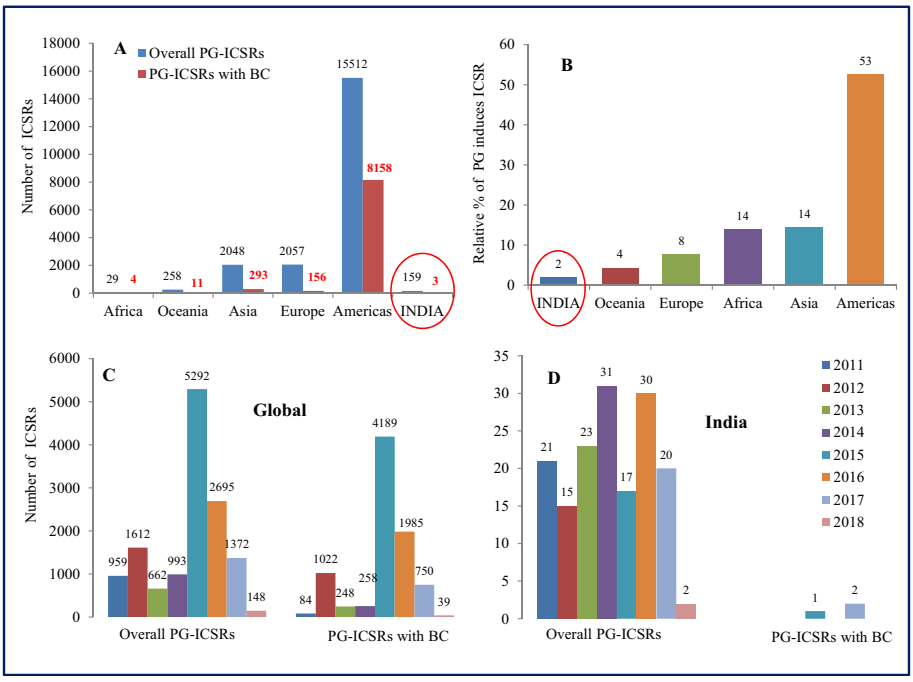

Figure 1. Distribution of pioglitazone-related individual case safety reports (PG-ICSRs) with respect to geography and yearly allocation. Distribution of overall and bladder cancer (BC)-specific PG-ICSRs (A), and relative percentage of bladder cancer (BC)-specific PG-ICSRs (B), by geographic region. Patterns of associated overall and BC-specific PG-ICSRs from 2011 to 2018, worldwide (C) and in India (D). Data from the VigiLyze pharmacovigilance database system.

bladder cancer. The prevalences of overall PG-ICSRs were similar in men and women, and of the 3 bladder cancer–associated PG-ICSRs, 2 were identified in men and 1 in a woman (Figure 2A). Therefore, the expected cases of bladder cancer associated with pioglitazone were found to be higher in the male population in both the global and Indian cohorts. Moreover, the prevalence of bladder cancer was higher among men in comparison to women; this finding is consistent with what has been reported in the literature.[10]

Distribution of PG-ICSRs Based on Age

Globally, the age group most reported was 45 to 64 years, although the number of reports without mention of the age was higher; in India, the age group that is most reported is 45 to 64 years for both overall and bladder cancer–associated PG-ICSRs (55% and 67%, respectively) (Figure 2B). Among the 3 cases of bladder cancer–specific PG-ICSRs in India, 2 cases were in the 45- to 64-year age group. Therefore, this age group was consistently reported to be most susceptible to pioglitazone-associated ADRs in both the worldwide and Indian cohorts. The age group least susceptible with regard to pioglitazone-associated BC-ICSRs was 18 to 44 years, which was supported by several studies in the scientific literature.[11]

Allocation of the Ten Most Frequently Reported Pioglitazone-associated ADRs, by System Organ Class

Worldwide, there were 33,375 overall pioglitazone-associated SOC reactions according to the *Medical Dictionary for Regulatory Activities* (MedDRA) nomenclature system, of which benign, malignant, or unspecified neoplasms (inclusive of cysts and polyps) SOC reactions contributed the most reports (9793 SOC reactions, 49.2%). In India, however, the SOC reaction of general disorders and administration site conditions had the highest number of reports (40%),

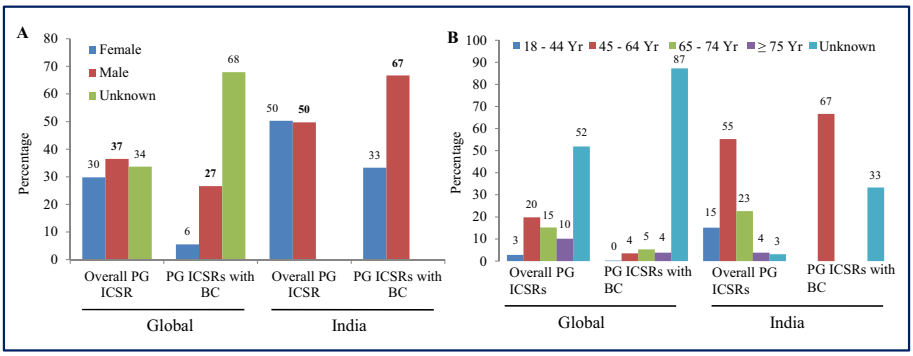

Figure 2. Distribution of overall and bladder cancer (BC)-specific pioglitazone-related individual case safety reports (PG-ICSRs), by sex and age. Of 159 PG-ICSRs from India, 3 were related to BC, whereas globally, of 19,904 PG-ICSRs, 8622 were related to BC. A, Worldwide and India-specific distributions of overall and bladder cancer–associated PG-ICSRs in male and female populations. Globally, there were significant reports of overall and bladder cancer–associated PG-ICSRs in patients whose sex was not recorded. B, Distribution of PG-ICSRs by age group, irrespective of sex. Globally, the greatest percentages of overall and bladder cancer–specific PG-ICSRs were in the 45–64-year age group. Data from the VigiLyze pharmacovigilance database system.

and benign, malignant, and unspecified neoplasms (inclusive of cysts and polyps) shared only 5% (eightfold less than the prevalence in the global cohort) (Figure 3A and B).

System organ classes (SOCs) are clusters of high-level terms grouped based on etiology, manifestation site or purpose. MedDRA is a clinically validated international medical terminology dictionary used by regulatory authorities in the pharmaceutical industry during the regulatory process from pre-marketing to post-marketing activities.[12] Of the 9793 benign, malignant, and unspecified neoplasm (inclusive of cysts and polyps) SOC reactions, there were 8592 bladder cancer–specific pioglitazone-associated SOC reactions and other similar terms, including bladder cancer not otherwise specified, bladder carcinoma, bladder carcinoma not otherwise specified, carcinoma bladder, invasive bladder cancer, malignant neoplasm of bladder, malignant neoplasm of bladder neck, malignant neoplasm of urachus, and urinary bladder carcinoma.

Top Five Co-reported or Concurrent Substances/ Drugs Reported in PG-ICSRs

Worldwide, 21,052 overall PG-ICSRs included concurrent substances/drugs. Metformin was the most frequently reported concurrently used drug associated with overall PG-ICSRs (5150 ICSRs, 26%) (Figure 3C). Worldwide, the concurrent distribution of metformin in bladder cancer–specific PG-ICSRs remained the same as for overall PG-ICSRs (25%) (Figure 3D). Similarly, in India, metformin was the most commonly reported concurrently used drug in all PG-ICSRs (64 ICSRs, 40%) (Figure 3E). Whereas, in India no concurrently used substance or drug was found to be associated with any of the 3 reported bladder cancer–specific PG-ICSRs. Thus, worldwide it was evident that metformin was the most widely administered concurrent drug associated with both overall and bladder cancer–specific PG-ICSRs.

Data Mining and Quality Review of Overall and Bladder cancer–specific PG-ICSRs

To evaluate the quality of ICSRs and for data mining, we analyzed the $N_{observed}$, $N_{expected}$, $N_{country}$, information components (ICs), and IC_{025} values of overall and bladder cancer–specific PG-ICSRs. The *IC* is an indicator value for disproportionate reporting when using the method for disproportionality analysis, developed by WHO-UMC. The IC value depends on the numbers of $_{observed}$ and $_{expected}$ ICSRs, where $N_{expected}$ is the number of case reports expected for the drug–effect combination, and $N_{observed}$ is the actual number of case reports for the drug–effect

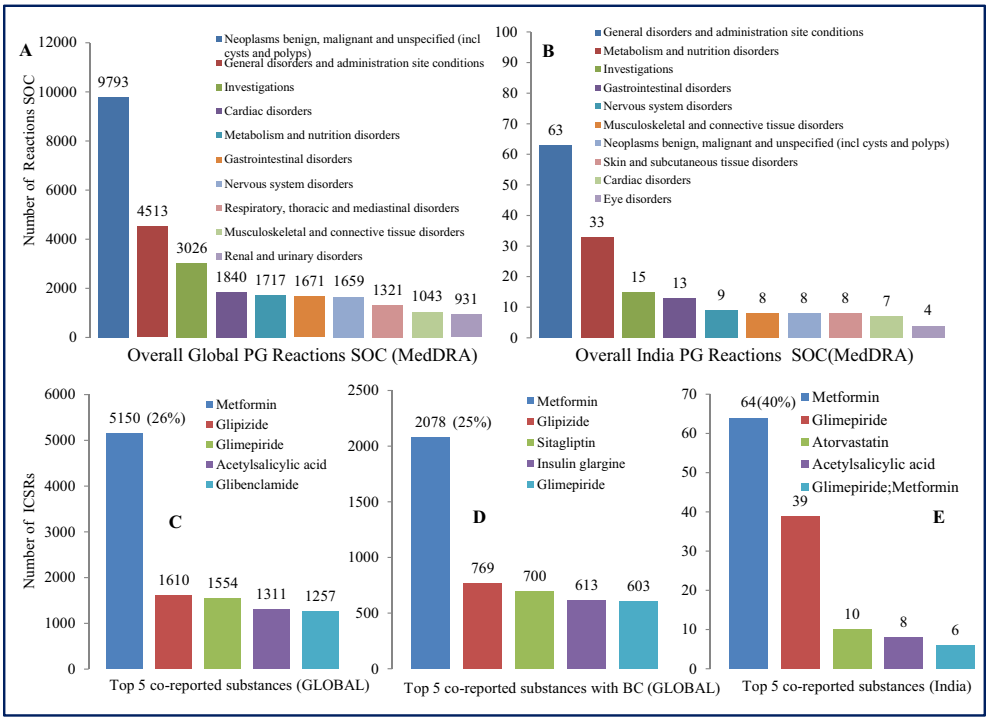

Figure 3. Most frequent adverse drug reactions, by system organ class (SOC), reported with pioglitazone (PG) use worldwide (A) and in India (B). In accordance with the World Health Organization's Medical Dictionary for Regulatory Activities (WHO-MedDRA), SOC reactions are presented using groups of high-level terms. Worldwide, 9793 benign, malignant, and unspecified neoplasms (inclusive of cysts and polyps) were reported with the use of PG, of which 8592 were bladder cancer (BC) specific. The 5 substances most frequently co-reported worldwide on PG-ICSRs overall (C) and specific to BC (D). Globally, metformin was most frequently reported concurrently used drug on PG-ICSRs both overall and specific to BC, while in India there were no reports of concurrently used drugs on PG-ICSRs with BC. Data from the VigiLyze pharmacovigilance database system.

combination. The pioglitazone-related reaction of weight increase had the highest $N_{observed}$ value (1190) and the reaction of death had the second highest $N_{observed}$ value (1029), which is contrary to the expected reactions (Figure 4A). The PG reactions with the highest $N_{expected}$ values, on the other hand, were nausea and pruritus (Figure 4B).

Pioglitazone-specific bladder cancer reaction had the highest IC (9.15) and IC_{025} (9.18) values, followed by bladder transitional cell carcinoma, bladder cancer recurrent, metastatic carcinoma of the bladder, and bladder neoplasm (Figure 4C). We further analyzed the PG reactions that were abundant in the maximum number of countries, and found that weight increase associated with pioglitazone was reported in 32 countries, whereas the bladder cancer reaction was reported in 27 countries (Figure 4D). In summary, all of the bladder cancer reactions related to pioglitazone use were received from 27 countries, with 8548 serious and 1858 fatal cases, and IC and IC_{025} values of 9.15 and 9.18, respectively (Figure 4E).

DISCUSSION

Pioglitazone, the most widely prescribed antidiabetic drug in the world, has been withdrawn from the markets by the French and German agencies due to the associated risk for bladder cancer. France's drug tolerability authority banned pioglitazone based on findings from a population-based cohort study that reported that "pioglitazone exposure was significantly associated with increased risk for bladder cancer."[5,13] Germany's Federal Institute for Drugs and Medical

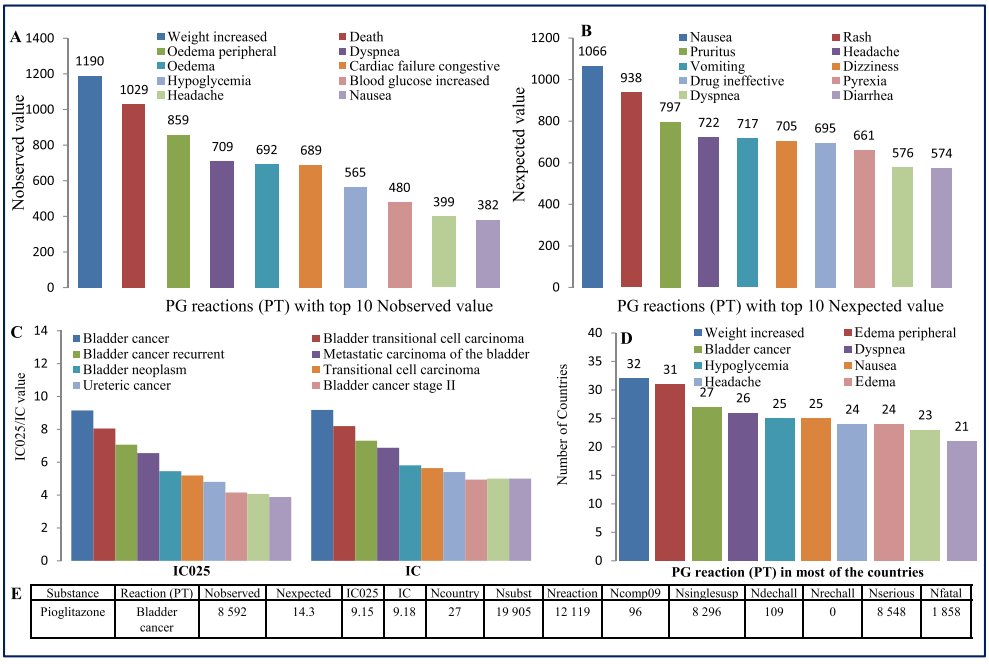

Figure 4. Data mining and quality parameters of PG-ICSRs. A and B, The 10 most frequently reported $N_{expected}$ and $N_{observed}$ values of PG-ICSRs, where $N_{expected}$ and $N_{observed}$ are the numbers of case reports expected for the drug—event pair and the actual number of case reports for the drug—event pair, respectively. Globally, the PG reactions of weight increase and nausea had the highest $N_{observed}$ and $N_{expected}$ values, respectively. C—E, Information component (IC) values and other statistical parameters of PG-ICSRs. The IC is a display value for disproportionate reporting that depends on the $N_{observed}$ and $N_{expected}$ values on ICSRs. PG-specific bladder cancer reaction accounts for the highest IC and IC_{025} values. Weight increase associated with PG was reported in 32 countries, and BC reaction was reported in 27 countries. Data from the VigiLyze pharmacovigilance database system. PT, preferred term.

Devices recommended suspension of the approval of pioglitazone use until further clarification after receiving results from the study by France's national health insurance body, which tracked patients on antidiabetic drugs between 2006 and 2009. However, interim results from a trial conducted by United States health insurer Kaiser Permanente have so far not confirmed a clear association between pioglitazone and bladder cancer. Another study, of data from Kaiser Permanente Northern California diabetes registry, reported that the use of pioglitazone for >2 years was weakly associated with an increased risk for bladder cancer.[14] A large-scale study from the United Kingdom reported no increase in bladder cancer with pioglitazone use.[15] The US FDA in June 2011 mandated the inclusion of information on the increased risk for bladder cancer in the pioglitazone labeling.[16] The decision was based on data from an interim analysis from the Kaiser Permanente Northern California diabetes registry and from a French population-based cohort study. However, pioglitazone still continues to be sold in most other major markets, including the United States, the United Kingdom, Japan, Canada, and India. At present, the US FDA and CDSCO advise the insertion of a bladder cancer risk advisory in the drug labeling, as well as patient counseling. Manufacturers must provide health care professionals with prescription-related advice in the drug's promotional literature stating that the drug should not be prescribed to people with active bladder cancer, a history of bladder cancer, or those with

uninvestigated hematuria. The relationship between cancer and DM reported in several epidemiologic studies suggests a higher risk for cancer in patients using insulin, a sulfonylurea, and/or an incretin-based therapy.[17] However, it is worth noting that type 2 DM and cancer share numerous potential risk factors, such as age, sex, obesity, physical activity, diet, alcohol use, and smoking habit. Insulin resistance, hyperinsulinemia, hyperglycemia-related oxidative stress, accumulation of advanced glycation products, and chronic low-grade inflammation are considered independent risk factors for cancer in type 2 diabetic patients.[17–20] Indian statistics illustrate that common malignancies associated with DM include uterine, ovary, and breast, but not bladder, cancer.

The present study analyzed the pattern of ADRs with pioglitazone use reported in WHO-UMC's VigiLyze pharmacovigilance database system a global database of ICSRs submitted by over 131 WHO member countries, including India. Among all of the worldwide ADRs related to pioglitazone, bladder cancer had the highest rate of occurrence (40%), with 8592 ICSRs, of which 3 cases were reported in India (0.03%). The Americas had the highest percentage of bladder cancer–specific ICSRs (53%), while India had a much lower percentage (2%). The Americas is clearly an outlier regarding the proportion of PG-ICSRs that are associated with bladder cancer: (8158/15,512 = 0.53), followed by Africa (4/29 = 0.14), Asia (293/2048 = 0.14), Europe (156/2057 = 0.075), Oceania (11/258 = 0.043), and India (3/159 = 0.019). There was nearly a 28-fold difference in the prevalence of pioglitazone-associated bladder cancer between the Americas and India. White people have about a twofold higher risk for bladder cancer compared to the African American and Hispanic populations. Asian Americans and Native Americans have slightly lower rates of bladder cancer compared to the above-defined populations. The reasons for these differences are not very well understood; considerations include genetic disposition, lifestyle, diet, and alcohol use. However, the low prevalence of bladder cancer with pioglitazone use in Indian patients may be due to the following reasons: (1) difference in genetic makeup of Indian with other ethnic groups; (2) less exposure to risk factors associated with bladder cancer (eg, smoking habit, advanced age, and low fluid intake); (3) prescribed lower therapeutic doses of pioglitazone because of the lower average body weight in the Indian population in comparison to people from Europe and the Americas (the mean therapeutic dose used in the Indian population is 15 to 30 mg/d); (4) inclusion of chemopreventive foods in the Indian diet, such as spices; (5) greater use of metformin as a concurrently used drug; and (6) under-reporting of ADRs in India in comparison to other countries.

In India, spontaneous reporting of ADRs by health care professionals is the cornerstone of pharmacovigilance. The major limitation associated with any spontaneous ADR reporting system is under-reporting. Under-reporting can be attributed to patient-related factors such as failure to recognize an ADR, an inability to link an ADR with the use of a specific drug, or possibly physician-related reasons. The reasons for poor reporting may also include financial incentives, legal aspects, an expectation that the serious ADRs are already documented when a drug is introduced into the market, the belief that a single report would make no difference, the belief that only serious ADRs are to be reported, and overload or lack of time. NCC-PvPI has taken steps to tackle under-reporting by addressing this issue in various forums and conferences, circulating a questionnaire form, and writing to professional bodies and scientific journals. Expanding on a point mentioned earlier, another possible explanation of the low prevalence of BC in the Indian population may be associated with the high content of spices in their diet. Indian spices, such as *Curcuma longa* (turmeric), *Nigella sativa* (black cumin), *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Crocus sativus* (saffron), *Piper nigrum* (black pepper), and *Capsicum annum* (chili pepper) contain important bioactive compounds, such as curcumin, thymoquinone, piperine, and capsaicin, which are known for their cancer preventive and therapeutic potential.[20] Moreover, pioglitazone is extensively metabolized by cytochrome P450 2C8. Therefore, several inhibitors and inducers of cytochrome P450 2C8, such as montelukast, zafirlukast, trimethoprim, gemfibrozil, and rifampicin, could alter the efficacy as well as the profile of adverse effects associated with pioglitazone when administered concurrently.[21]

Worldwide, the prevalence of overall PG-ICSRs was highest in the year 2015 (27%), affecting mostly men

between the ages of 45 and 64 years (37%), whereas all PG-ICSRs were equally distributed in 2014 and 2016, affecting primarily men of the same age group. We found that the prevalences of pioglitazone-associated bladder cancer were higher in men and in older individuals compared to those in women and younger individuals, findings consistent with those from previously published scientific reports.[10,22–24] Possible explanations for the excess risk in men include environmental and dietary exposures, innate sexual characteristics such as urination habits or hormone-related factors, or high nicotine use or exposure to other carcinogens, which are known to be major risk factors for bladder cancer.[25] However, based on the limited available information, we cannot conclude whether the risk for bladder cancer associated with pioglitazone use is due to an active pharmaceutical ingredient, a pharmaceutical component of prescribed dosage formulations, or active pharmaceutical ingredient–excipient interactions.

As per the nomenclature system of MedDRA, there were 33,375 pioglitazone-related SOC reactions, of which 8592 were pioglitazone-related bladder cancer–specific SOC reactions. MedDRA is a clinically validated international medical terminology dictionary used by regulatory authorities in the pharmaceutical industry during the regulatory process from pre-marketing to post-marketing activities.[12] The quality of reported ICSRs depends on several factors, such as $N_{observed}$, $N_{expected}$, $N_{country}$, ICs, and IC_{025} values. The PG-specific bladder cancer reaction had the highest IC/IC025 value, along with the second-highest occurrence in 27 countries, including 8548 serious and 1858 fatal cases. On the other hand, the pioglitazone-related reaction of death had the second-highest $N_{observed}$ value (1029).

Metformin administered concurrently with pioglitazone has been associated with one fourth of overall and bladder cancer–specific PG-ICSRs worldwide, whereas in India, pioglitazone has been associated with the highest rate of concurrent use in overall PG-ICSRs (40%), but its use was not reported with bladder cancer–specific PG-ICSRs. Overall, this finding could mean that, worldwide, from a total of 8592 bladder cancer–specific PG-ICSRs, 2078 ICSRs (24%) listed metformin as a concurrent drug, 5436 ICSRs (63%) listed a concurrent drug(s) other than metformin, and 978 ICSRs (12%) listed no concurrent drugs. Therefore, globally, around 24% of bladder cancer–specific PG-ICSRs occurred with metformin use, and in India, the rate was 40%, with no reports of bladder cancer–specific PG-ICSRs. In India, a significantly higher proportion of PG-ICSRs occurred with metformin use, which may be a factor contributing to the low prevalence of bladder cancer–specific PG-ICSRs. Accumulated preclinical and clinical evidence suggests that metformin may restrain *in vitro* proliferation and growth of tumor cells and reduce cancer risk in diabetic patients, raising the possibility of future uses of metformin as an anticancer therapeutic.[26,27] It has been found that patients with nonmuscle invasive bladder cancer and DM who did not take metformin had significantly shorter recurrence-free and progression-free survival times than did their counterparts without DM or those with DM taking metformin.[26] However, the exact mechanism of this finding is still not clear and is an area of ongoing research efforts. Metformin treatment of cancer cells induces degradation of an enzyme called *mammalian target of rapamycin* (mTOR), which has been shown to correlate with the inhibition of proliferation and migration of cancer cells.[28]

mTOR is a serine/threonine kinase that is ubiquitously expressed in cells to regulate growth and metabolism.[29] Thus, the dysregulation of the mTOR pathway has been shown to be important in an increasing number of diseases, including cancer, type 2 DM, and neurodegeneration.[30,31] Moreover, both metformin and pioglitazone inhibit P-glycoprotein (P-gp) efflux activity *in situ* in a dose-dependent manner and down-regulate P-gp expression *in vitro*. P-gp is a transmembrane drug efflux pump, and drugs that act as P-gp inducers and inhibitors may affect drug–drug interactions when drugs are coadministered.[32] Therefore, the findings from these studies suggest that diabetic patients treated with PG along with metformin may not have an increased risk for bladder cancer, and that pioglitazone use in diabetic patients with diagnosed bladder cancer may not promote tumor progression, but may actually inhibit tumor development, although the majority of the available studies assessing the effects of anti-diabetic medications on cancer development have significant limitations, primarily because they did not account for confounding factors.

The present study had an important limitation, spontaneous reporting of ADRs, which may have led

to under-reporting of relevant information, including bladder cancer–specific PG-ICSRs in India. A *spontaneous report* of an ADR is an unsolicited communication by health care professionals, pharmaceutical companies, or consumers to the NCC-PvPI. However, spontaneous reporting shows several limitations, which are mainly related to under-reporting, variable quality of the reported data, and a lack of information on drug exposure. Therefore, strong conclusions cannot be made and the results presented may not be significantly generalizable in reference to other geographic areas with different epidemiologic or clinical settings.

CONCLUSIONS

Several past clinical studies have proposed pioglitazone as a good candidate for the treatment of diabetic patients with high insulin resistance and a high risk for, or history of, cardiovascular disease. India has a very low occurrence of overall and bladder cancer–specific pioglitazone-induced ADRs in comparison to Europe and the Americas. The reporting of PG-ICSRs was highest in the year 2015 and mostly affected men between 45 and 64 years of age. Metformin was reported as the most frequently used concurrent drug, and the most abundant reaction reported in PG-ICSRs was weight increase, present in 32 countries, followed by bladder cancer (27 countries), both with very high IC values. The low prevalence of PG associated BC ICSRs in India may have been associated with differences in genetic makeup, low exposure to risk factors for bladder cancer, prescription of low therapeutic doses of pioglitazone, presence of chemopreventive spices in the Indian diet, higher concurrent use of metformin, and under-reporting of ADRs. Metformin itself has anticancer potential, and its use along with pioglitazone may contribute to the prevention of bladder cancer. There is a lot of debate about the benefit–risk evaluation of pioglitazone. However, the balance of benefits and risks for a drug can change over time as new knowledge and data on the effects of a drug when used in the general population or during postmarketing surveillance are accumulated. Most significantly, while a relationship between cancer and diabetes medications has been discussed for over a decade, the present evidence does not support immediate changes in the use of pioglitazone in clinical practice, nor does the evidence support a significant link with bladder cancer in the Indian population, although the present study had relatively few bladder cancer–specific PG-ICSRs in India; for firm conclusions, a longer follow-up study in this cohort would be required.

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The information presented in this study comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug related is not the same in all cases. However, the result, analysis, statement, and conclusions expressed herein are those of the authors and do not necessarily represent the opinions of the WHO-UMC or the PvPI-NCC of India. Moreover, submission of these ADR reports does not constitute an admission that medical personnel, the manufacturer, or the product caused or contributed to the reaction.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I, et al. Freddie bray bladder cancer incidence and mortality: a global overview and recent trends. *Eur Urol*. 2017;71:96–108.
2. Kuo HW, Tiao MM, Ho SC, et al. Pioglitazone use and the risk of bladder cancer. *Kaohsiung J Med Sci*. 2014;30:94–97.
3. Smith U. Pioglitazone: mechanism of action. *Int J Clin Pract Suppl*. 2001;121:13–18.

4. Zhu C, Xiao Y, Liu X, et al. Pioglitazone lowers serum retinol binding protein 4 by suppressing its expression in adipose tissue of obese rats. *Cell Physiol Biochem*. 2015;35:778–788.
5. 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;34:916–922.
6. Rolfes L, Van HF, Taxis K, et al. The impact of experiencing adverse drug reactions on the patient's quality of life: a retrospective cross-sectional study in The Netherlands. *Drug Saf*. 2016;39:769–776.
7. Kalaiselvan V, Prakash J, Singh GN. Pharmacovigilance programme of India. *Arch Pharm Pract*. 2012;3:229–232.
8. Kalaiselvan V, Thota P, Singh GN. Pharmacovigilance programme of India: recent developments and future perspectives. *Indian J Pharmacol*. 2016;48:624–628.
9. Kumar P, Kaur I, Kalaiselvan V, et al. Safety monitoring of local anaesthetic drugs from the perspective of pharmacovigilance programme of India. *Indian J Anaesth*. 2017;61:534–537.
10. Hartge P, Harvey EB, Linehan WM, et al. Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst*. 1990;82:1636–1640.
11. Madeb R, Messing EM. Gender, racial and age differences in bladder cancer incidence and mortality. *Urol Oncol*. 2004;22:86–92.
12. Merrill GH. The MedDRA paradox. *AMIA Annu Symp Proc*. 2008;6:470–474.
13. Neumann A, Weill A, Ricordeau P, et al. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia*. 2012;55:1953–1962.
14. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR, Troostenburg PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Saf*. 2009;32:187–202.
15. Wei L, MacDonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. *Br J Clin Pharmacol*. 2013;75:254–259.
16. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-ongoing-safety-review-actos-pioglitazone-and-increased-risk. Accessed June, 2011.
17. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33:1674–1685.
18. Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia*. 2009;52:1699–1708.
19. Smith U, Gale EA. Cancer and diabetes: are we ready for prime time? *Diabetologia*. 2010;53:1541–1544.
20. Zheng J, Zhou Y, Li Y, et al. Spices for prevention and treatment of cancers. *Nutrients*. 2016;8:E495.
21. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 2005;55:10–30.
22. Horn EP, Tucker MA, Lambert G, et al. A study of gender-based cytochrome P450 1A2 variability: a possible mechanism for the male excess of bladder cancer. *Cancer Epidemiol Biomarkers Prev*. 1995;4:529–533.
23. Wan J, Grosman HB. Bladder carcinoma in patients age 40 years or younger. *Cancer*. 1989;64:178–181.
24. Augustine A, Hebert JR, Kabat GC, et al. Bladder cancer in relation to cigarette smoking. *Cancer Res*. 1988;48:4405–4408.
25. Jaakkola T, Laitila J, Neuvonen PJ, et al. Pioglitazone is metabolised by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors. *Basic Clin Pharmacol Toxicol*. 2006;99:44–51.
26. Yang S, Wang J, Chen M, et al. Pioglitazone use and risk of bladder cancer: an in-vitro study. *Int J Med Sci*. 2018;15:228–237.
27. Rieken M, Xylinas E, Kluth L, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. *BJU Int*. 2013;112:1105–1112.
28. Alalem M, Ray A, Ray BK. Metformin induces degradation of mTOR protein in breast cancer cells. *Cancer Med*. 2016;5:3194–3204.
29. Gomez-Pinillos A, Ferrari AC. mTOR signaling pathway and mTOR inhibitors in cancer therapy. *Hematol Oncol Clin North Am*. 2012;26:483–505.
30. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell*. 2012;149:274–293.
31. Karar J, Maity A. PI3K/Akt/mTOR pathway in angiogenesis. *Front Mol Neurosci*. 2011;4:51.
32. Abbasi MM, Valizadeh H, Hamishehkar H, et al. Inhibition of P-glycoprotein expression and function by anti-diabetic drugs gliclazide, metformin, and pioglitazone *in vitro* and *in situ*. *Res Pharm Sci*. 2016;11:177–186.

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