

Pioglitazone: Indian perspective

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ABSTRACT

Pioglitazone was approved in 1999 as an adjunct to exercise and diet to improve glycemic control in adults with type 2 diabetes mellitus, primarily by reducing insulin resistance. Beyond these effects on glucose metabolism, pioglitazone has positive effects on lipid metabolism, blood pressure, endothelial function, adiponectin, and C-reactive protein levels. These make pioglitazone treatment effective beyond glucose control. Pioglitazone generally has been viewed as a safer option for patients who warrant treatment with a thiazolidinedione-class drug. There has been some recent data on cancer incidence in patients on pioglitazone, which is currently being reviewed by drug regulatory authorities in the United States and in Europe. Given the benefits of pioglitazone, alone and in combination, it would be appropriate to continue judicious use of the drug in patients who may benefit from its use.

Key words: Bladder cancer, cardiovascular benefits, India, pioglitazone

INTRODUCTION

It has long been known that type 2 diabetes is a disorder involving multiple components: insulin resistance, an insulin secretory defect, and an increase in hepatic glucose production. Patients with type 2 diabetes express varying degrees of these defects.^[1]

Targeting insulin resistance and/or hepatic glucose production was first made possible with the introduction of metformin. Metformin has been available worldwide since 1957 and was introduced into the U.S. market in 1995.^[1]

Subsequently, thiazolidinediones were introduced about a decade ago. The thiazolidinediones (also known as glitazones) or peroxisome-proliferator-activated receptors agonists improve glycemic control by increasing insulin sensitivity in fat, liver, and muscle, and may have a role in β cell protection.^[2]

HISTORY OF GLITAZONES

Ever since their introduction, the glitazones have had a stormy history. Troglitazone, the first in the glitazone class of drugs, was launched in the USA in March, 1997. It reached Europe later that year, only to be withdrawn within weeks on the grounds of liver toxicity. Meanwhile it went on to generate sales of over \$2 billion in the USA, and caused at least 90 cases of liver failure (70 resulting in death or transplantation) before it was withdrawn in March 2000. Rosiglitazone and pioglitazone reached the U.S. market in 1999 as first-line agents to be used alone or in combination with other drugs.^[3]

Currently, only pioglitazone is available for use as a single agent or in combination with metformin or sulphonylureas.

GLITAZONES AND CARDIOVASCULAR DISEASE

Initial trials, prior to licensing of both rosiglitazone and pioglitazone, concentrated primarily on biochemical endpoints related to glycemic control rather than clinical outcomes. The safety and tolerability assessed were short term.^[4]

Safety with respect to cardiovascular disease was not noted. Since cardiovascular events are a late complication of diabetes, the initial trials were not long enough to

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identify any difference in cardiovascular outcomes between treatment groups.^[4]

More recently, however, there have been concerns that rosiglitazone may be associated with an increased cardiovascular risk.

ROSIGLITAZONE: CURRENT STATUS

In 2007, a meta-analysis of controlled clinical trials found increases in the risk of myocardial infarction and a near-significant increased risk of death from cardiovascular causes when rosiglitazone was compared with placebo or with standard diabetes drugs.^[5]

In July 2010, the Health Ministry of India ordered Glaxo Smith Kline to suspend human studies being conducted in 19 sites across India. Subsequently, in October 2010, the Drug Controller General of India (DCGI) proposed to the Health Ministry to ban rosiglitazone.^[6]

In September 2011, the European Medicines Agency (EMA) recommended the suspension of marketing authorization of rosiglitazone, with the EMA's Committee for Medicinal Products for Human Use (CHMP) stating that "the benefits of rosiglitazone no longer outweigh the risks."^[7]

In May 2011, the U.S. FDA placed several restrictions on the prescribing and use of rosiglitazone. Healthcare providers and patients in the USA must enroll in a special program in order to prescribe and receive these drugs. These new restrictions are part of a Risk Evaluation and Mitigation Strategy (REMS)—a program FDA may require to manage serious risks of marketed drugs.^[8]

The REMS limits the use of rosiglitazone medicines to patients already being successfully treated with these medicines and patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines.

PIOGLITAZONE AND CARDIOVASCULAR EFFECTS

Pioglitazone, the other thiazolidinedione, on the other hand has not attracted the same degree of controversy as rosiglitazone with regard to risk of myocardial infarction. In fact there is an increasing amount of evidence to support a modest cardioprotective role in terms of ischemic events for pioglitazone in patients with type 2 diabetes.

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), enrolled over 5000

patients in 19 European countries involving over 320 investigators to investigate whether pioglitazone can prevent the progression of macrovascular disease, which is associated with cardiovascular events such as myocardial infarction in type 2 diabetes patients.^[9]

The results showed that there was a non-significant 10% risk reduction in the primary end point of all-cause mortality, non-fatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle with pioglitazone relative to placebo (HR 0.90, 95% CI 0.80–1.02, $P=0.095$). There was a significant 16% risk reduction in the main secondary end point of all-cause mortality, non-fatal MI, and stroke with pioglitazone relative to placebo (HR 0.84, 95% CI 0.72–0.98, $P=0.027$).^[9]

In fact, no study has ever indicated elevated risk of acute ischemic events with pioglitazone, unlike the accumulated data for rosiglitazone. A key difference between the two thiazolidinediones is that pioglitazone improves lipids, whereas rosiglitazone has shown a greater than 10% elevation in LDL cholesterol.^[10]

Furthermore, pioglitazone affects a diverse array of metabolic and inflammatory processes potentially relevant to CV disease pathophysiology, including key metabolic risk factors (dyslipidemia, hyperglycemia, hypertension), insulin resistance, endothelial dysfunction and inflammatory cytokines, markers of plaque stability, adhesion molecules, and mediators of coagulation/fibrinolysis.^[11]

Furthermore, pioglitazone remains in the ADA/EASD consensus group recommendations as well as AACE as a second tier agent for type 2 diabetes.^[12]

GLITAZONES AND CANCER

Recently, a controversy has been raised of an apparent risk of bladder cancer in patients on pioglitazone.

Two studies were published simultaneously in the April 2011 issue of the journal *Diabetes Care*. One study^[13] explored the risk of incident cancer at the 10 most common sites, namely prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma [NHL], pancreas, kidney/renal pelvis, rectal, and melanoma in patients on pioglitazone.

A cohort study of 252,467 patients aged ≥ 40 years from the Kaiser Permanente Northern California Diabetes Registry was conducted.

The authors of this study^[14,15] concluded that no clear

evidence of an association between use of pioglitazone and risk of the incident cancers was found.

The second study focused on cases of bladder cancer recorded in the FDA Adverse Event Reporting System (AERS) database associated with antidiabetic drug treatment. This study analyzed the AER from 2004 to 2009, involving antidiabetic drugs.

According to the reports the reporting odds ratio (ROR) of bladder cancer was significantly >1 for pioglitazone (ROR 4.30 [95% CI 2.82–6.52]; $P < 0.001$) as well as for gliclazide and acarbose. Among the 31 cases of bladder cancer reported in pioglitazone users (mean age, 70 years; range 53–84), 23 occurred in men (3.86 [2.37–6.26]) and 8 were in women (5.19 [2.15–12.11]). When stratified by age (cutoff, 65), ROR for pioglitazone was only significant in older patients (5.10 [3.14–8.23]). Four cases of bladder cancer were reported in 2004, three in 2005, nine in 2006, five in 2007, six in 2008, and four in 2009.

However, the authors themselves admitted that the ROR analysis has several limitations, including generic under-reporting, over-reporting generated by notoriety bias, dependence on the drug-marketing period (Weber effect), missing or misspelled data, and lack of information on patients' habits (smoking) or occupational risks.

Furthermore, they also suggest more case-controlled studies to validate these results.

DIABETES AND CANCER

The association between cancer and type 2 diabetes is not new. Epidemiological studies, although inconclusive,^[16] have raised concerns about the increased risk of malignancies in type 2 diabetes patients associated with the use of antidiabetic medications. Some publications have suggested a higher risk of cancer in patients receiving insulin, sulfonylureas, and incretin-based therapies. Yet, the majority of the available studies assessing the effect of antidiabetic medications on cancer development have significant limitations, mainly because they did not take confounding factors into account. On the other hand, preclinical, epidemiological, and clinical evidence suggests that metformin appears to inhibit proliferation and growth of some tumor cells *in vitro* and reduces cancer risk in diabetics in the clinical setting, raising the possibility for future use of metformin in the treatment of malignancies in humans.

Furthermore, it is well known that some types of cancer are more common in type 2 diabetes. This association was first reported as an incidental finding in 1932. It has been observed that diabetics have a higher risk of malignancy, specially cancer of the pancreas, liver, endometrium, breast,

colon, rectum, and urinary bladder. However, the incidence of other types of cancer (e.g., lung, kidney, non-Hodgkin lymphomas) do not seem to be strongly associated with diabetes or the evidence is inconclusive.^[16]

Moreover, the exact mortality rate attributable to cancer in diabetics remains unknown and it is possible that higher mortality risk associated with chronic hyperglycemia is independent of cancer.

It is also important to note that type 2 diabetes and cancer share several common potential risk factors (e.g., aging, sex, obesity, physical activity, diet, alcohol, and smoking). In type 2 diabetes, insulin resistance and hyperinsulinemia (either endogenous due to insulin resistance or induced by administration of exogenous insulin formulations) are considered to be independent risk factors for cancer development.^[17]

In addition, hyperglycemia-related oxidative stress, accumulation of advanced glycation end products on proteins, and other macromolecules as well as chronic low-grade inflammation may also enhance the risk of malignant transformation.^[18,19]

Most importantly while an association between cancer and type diabetes and related medications has been debated for over five decades, there is an agreement that the available evidence does not suggest any imminent significant change in clinical practice.

CANCER IN INDIA

Statistics show that the head and neck cancers, cervical cancer and breast cancer are the most common cancers in India.^[20] Hyperglycemia related malignancies such as those of the uterus, ovary and breast, are far more common in India than a malignancy of the bladder. Goal directed glycemic control thus remains the main focus of management in type 2 diabetes.

According to a study published in 2001, incidence rates for bladder cancer are low in Indian men, varying from 2.6 to 4.8 per 100,000 in urban areas, and the site does not figure among the ten most common ones.^[21]

As per the Indian cancer registry data in men, it is the ninth most common cancer accounting for 3.9% of all cancer cases in Maharashtra.^[22]

PIOGLITAZONE: CURRENT STATUS

The European Medicines Agency ("EMA")^[23] acknowledged in a statement on June 9, 2011 that: "While review of

pioglitazone is ongoing, the Committee for Medicinal Products for Human Use (CHMP) is not recommending any changes to the use of pioglitazone-containing medicines.”

On 21/07/2011 after finalising its review, the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) issued an alert based on its own review, concluding that the benefit versus risk balance of pioglitazone remains positive for a limited population of type 2 diabetics. They concluded that the small increased risk of bladder cancer could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual patient’s treatment.

Almost at the same time, the Food and Drug Administration has updated the label for pioglitazone (Actos, Takeda) to highlight the risk of cancer. The updated label states that pioglitazone should not be started in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

Like the FDA, the EMA also concluded that pioglitazone should not be considered in patients with current or a history of bladder cancer or those with uninvestigated macroscopic hematuria.

CONCLUSIONS

Currently, the U.S. FDA recommendations are mainly restricted to patients of bladder cancer. FDA recommends that healthcare professionals should not use pioglitazone in patients with active bladder cancer and use pioglitazone with caution in patients with a prior history of bladder cancer.^[24]

The U.S. FDA has announced that it will continue to evaluate data from the ongoing 10-year epidemiological study and conduct a comprehensive review of the results from the French study as well.

Clearly more studies are needed, probably focused on the Indian population. It is also important that physicians recognize the early signs and symptoms of cancer including bladder cancer.

At the same time, it is important to recognize the benefits of pioglitazone and use it judiciously in appropriate patients who would benefit from the use of this drug.

REFERENCES

- Peters AL. Using Thiazolidinediones: Rosiglitazone and pioglitazone in clinical practice. *Am J Manag care* 2001;7 (3 Suppl):S87-95; quiz S96-7.
- Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med* 2004;351:1106-18.
- Gale EA. Lessons from the glitazones: A story of drug development. *Lancet* 2001;357:1870-5.
- Taylor C, Hobbs FD. Type 2 diabetes, thiazolidinediones, and cardiovascular risk. *Br J Gen Pract* 2009;59:520-4.
- 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 [Erratum, *N Engl J Med* 2007;357:100.]
- <http://www.indianexpress.com/news/dcgi-wants-health-to-ban-diabetes-drug/704098/>, [Last accessed on 2011 July 07].
- <http://www.theheart.org/article/1163219.do>, [Last accessed on 2011 July 07].
- <http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm>, [Last accessed on 2011 Jun 27].
- <http://www.medpagetoday.com/MeetingCoverage/ADA/21009>, [Last accessed on 2011 Jun 27].
- <http://www.proactive-results.com/html/analysis.htm> [Last accessed on 2011 Jun 27].
- Erdmann E, Wilcox R. Pioglitazone and mechanisms of CV protection. *QJM* 2010;103:213-28.
- AACE Diabetes Care Plan Guidelines. *Endocr Pract* 2011;17 (Suppl 2): 3-53.
- Ferrara A, Lewis JD, Quesenberry CP Jr, Peng T, Strom BL, Van Den Eeden SK, *et al.* Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care* 2011;34:923-9.
- Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916-22.
- Piccinni C, Motola D. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care* 2011;34:1369-71.
- Drzewoski J, Drozdowska A, Sliwińska A. Do we have enough data to confirm the link between antidiabetic drug use and cancer development? *Pol Arch Med Wewn* 2011;121:81-7.
- Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia* 2009;52:1699-708.
- Smith U, Gale EA. Cancer and diabetes: Are we ready for prime time? *Diabetologia* 2010;53:1541-4.
- Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, *et al.* Diabetes and cancer: A consensus report. *Diabetes Care* 2010;33:1674-85.
- Available from: <http://www.cpaaindia.org/activities/detection.htm>, [Last accessed on 2011 Jul 07].
- Notani PN. Global variation in cancer incidence and mortality. *Curr Sci* 2001;81:465-74.
- Yeole BB, Kurkure AP, Koyande SS. Geographic variation in cancer incidence and its patterns in urban Maharashtra, 2001. *Asian Pac J Cancer Prev* 2006;7:385-90.
- European Medical Agency [22.07.2011] Update on ongoing European review of pioglitazone-containing medicine.
- Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm>, [Last accessed on 2011 Jul 07].

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