

Point of View



Pioglitazone and Bladder Cancer: The Pros and Cons

Vijay Panikar*

Pioglitazone is the only drug, that best addresses the main pathophysiological defect in type 2 diabetes i.e insulin resistance, Glitazones are a better alternative to metformin or glibenclamide as monotherapy with long term durability of glucose lowering effect (ADOPT trial).¹ The PERISCOPE trial,² CHICAGO trial, PIPOD study and many more have shown that pioglitazone was associated with improvement in CV risk factors and prevention of atherosclerosis progression. PROACTIVE study³ showed that pioglitazone improved glycaemic control and additionally suggested a possible cardio-protective effect.

AFSSAPS the French regulatory authority followed by Germany on June 9, 2011 suspended the use of pioglitazone containing products for the treatment of type 2 diabetes in France. The decision to suspend the two products was taken on the basis of a small increased risk with statistical significance of bladder cancer in patients treated with pioglitazone observed in a French database study (CNAMTS) independently conducted by French authorities. It recommends that patients currently treated with pioglitazone do not stop their treatment and consult their physician to adapt their diabetes treatment.

The European Medicines Agency ("EMA")⁴ 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."

In order to fully appreciate the significance of this issue, we must first review some basic information about bladder cancer and the prevalence of bladder cancer in the general population. Incidence rates for bladder cancer are low in Indian men, varying from 2.6 - 4.8/100,000 in urban areas.⁵

Bladder cancer is estimated to occur in 20 per 100,000 persons per year in the United States and is thought to be higher in diabetics and Caucasians. This equals 1/5000 (<http://www.cancer.gov/statistics>). An estimated 70,530 new cases of bladder cancer cases were diagnosed in 2010.

It is more common in men than women. The most common type of bladder cancer is Urothelial carcinoma, comprising 90-95% of all bladder cancers and is strongly associated with cigarette smoking. Adenocarcinoma of the bladder comprises about 2% of all bladder cancers and is most commonly associated with prolonged inflammation and irritation. Squamous cell carcinoma comprises 1-2% of bladder cancers and is associated with longstanding stones in the bladder and chronic infection and inflammation. The prognosis of bladder cancer is determined by the stage and grade of the tumor. Low risk bladder cancer does not impact the life expectancy of the patient. High risk cancer has the potential to metastasize which will impact the life expectancy. The recent pioglitazone data does not highlight what kind of bladder cancer was increased in the diabetic patient.

The PROactive study found a nonsignificant excess of bladder tumors among patients treated with pioglitazone.

In 2003, the U.S. FDA requested that the manufacturer of pioglitazone conduct a safety study to assess whether therapy with pioglitazone increases the risk of bladder cancer. Takeda, is conducting a ten-year, observational cohort study as well as a nested case-control study in patients with diabetes who are members of Kaiser Permanente Northern California (KPNC)⁶ health plan. Patients selected in this study had diabetes mellitus and were ≥ 40 years of age at study entry. Patients with bladder cancer prior to study entry or within six months of joining KPNC were excluded from this study. The cohort included 193,099 patients with diabetes. A planned five-year interim analysis was performed with data collected from January 1, 1997 through April 30, 2008. The median duration of therapy among pioglitazone-treated patients was 2 years (range 0.2-8.5 years). The study investigators did not observe a statistically significant association between any pioglitazone exposure and increased bladder cancer risk in the study (Hazard ratio = 1.2, 95% Confidence Interval: 0.9-1.5). However, the risk of bladder cancer increased with increasing dose >28000 mg and duration of pioglitazone use, reaching statistical significance after 24 months of exposure.

On 21/07/2011 after finalising its review, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) confirmed that these medicines remain a valid treatment option for certain patients with type 2 diabetes but that there is a small increased risk of bladder cancer in patients taking these medicines. However, the CHMP also concluded that the small increased risk 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.

The CHMP concluded that the evidence from different sources shows that there is a small increased risk of bladder cancer with pioglitazone. Recently available data from epidemiological studies (Kaiser Permanente Northern California cohort study, French CNAMTS cohort study, GPRD case control study) point to a small increased risk (relative risk ranging from 1.12 to 1.33) of bladder cancer in diabetic patients treated with pioglitazone, in particular in patients treated for the longest durations (more than 2 years) and with the highest cumulative doses (more than 28000mg).

In line with the recommendations of the SAG, the CHMP concluded that there are some patients who cannot be adequately treated by other treatments and who will benefit from treatment with pioglitazone. The CHMP agreed that it was not possible to further restrict the current indications of pioglitazone. Instead, prescribers are advised to carefully select patients and monitor response to treatment. In patients responding to treatment, the CHMP concluded that the benefits outweigh the risks.

The CHMP agreed that there is a need for further analysis of the types, evolution and severity of bladder cancer in patients treated with pioglitazone compared to diabetics not treated with pioglitazone. It remains unclear as to whether it is an early effect or a risk with prolonged use/high cumulative dose. Therefore,

*Prof. of Medicine, K.J. Somaiya Medical College, Mumbai; Consultant, Dept. of Endocrinology and Diabetes, Lilavati Hospital, Mumbai

the CHMP has asked the marketing authorisation holder to conduct a pan-European epidemiological study focusing on more robust characterisation of the risk, in particular the risk period and risk with increasing age, to inform the evidence-base for risk minimisation measures.

Prescribers are advised not to use these medicines in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. In light of age-related risks, the balance of benefits and risks should be considered carefully both before initiating and during treatment in the elderly. Prescribers should review the treatment of patients on pioglitazone after three to six months (and regularly afterwards) to ensure that only patients who are deriving sufficient benefit continue to take it.

Conclusion

India is the capital of diabetes and Indians as an ethnic group have very high levels of insulin resistance which by itself is a major risk factor for cardiovascular complications.

The major correlation between pioglitazone and bladder cancer is the duration of therapy > 24 months and cumulative dose of > 28000 mg which means the average daily dose of pioglitazone is about 40 mg/day. The doses used in the US and Europe are 30 -45 mg/day, We in India generally do not use doses greater than 15 mg, which means to achieve a cumulative dose of 28000 mg we would take 5 years and if we use 7.5 mg^{8,9} it would take 10 years. Low dose pioglitazone has of late become very popular in India due to its efficacy and lesser side effects like weight gain and fluid retention

Cardiovascular disease prevention often requires long term use of pharmaceutical intervention, The PROACTIVE data demonstrates that 11.3% of 2605 diabetics on pioglitazone had a CV death, MI, stroke or ACS= 294, 13.9% of 2603 diabetics not on pioglitazone had a CV death, MI, stroke or ACS = 361. Therefore, 66 fewer events in 2.8 years or 23 fewer events per year per approx. 5,000 diabetics occurred in the pioglitazone arm. Comparing with bladder cancer, it is accepted that about one diabetic out of 5,000 per year will get bladder cancer regardless of glycemic treatment. Appreciating pioglitazones' benefit of heart attack and stroke prevention, it would have to increase the risk of bladder cancer about 20 fold to offset the intended cardiovascular benefit.

Probably the official agency rendering judgment on pioglitazone are only considering its benefit as one of sugar control, as this is its only formal indication. We are in a different position because our use of pioglitazone also includes the prevention of CV events and diabetes. Therefore, we must weigh the risk to benefit ratio on that basis.

Today patients are relatively well informed due to the media and internet and if they were to ask regarding the risk of bladder cancer what would I answer?

I would tell the patient that on the basis of the recent studies, there seems to be a very small increased risk for bladder cancer, but at the same time, there seems to be a lower risk (for instance,

in the PROACTIVE study on cardiovascular endpoints and some other studies), for other cancers such as breast cancer. On balance, it is just not a big threat to the patient with diabetes.

We have numerous choices of drugs, so if it is a really big concern to patients, I would much rather, in a controlled fashion, take them off the drug and put them on another drug. I would always tell them that frankly, we're shifting things around, and it's not clear that shifting the drug is going to result in a better outcome for them than the drug that they are on today.

US FDA recommendations:

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.
- Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.

EMA recommendations:

Prescribers are advised not to use these medicines in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria. They should also consider the age of the patient and review the treatment after three to six months "and regularly afterwards".

References

1. Levy D, Viberti G, Kahn S, et al. A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2002;25:1737-1743.
2. Nissen SE, Nicholls SJ, Wolski K, et al. PERISCOPE Investigators. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE randomized controlled trial. *JAMA* 2008;299:1561-73.
3. Dormandy JA, Charbonnel B, Eckland DJ, et al. PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes: a randomized trial of pioglitazone. The PROactive Study
4. European Medical Agency [22.07.2011] Update on ongoing European review of pioglitazone-containing medicine.
5. Gupta P, Jain M, Kapoor R. Impact of age and gender clinicopathological characteristics of bladder cancer. *Indian J Urol* 2009;25:207-210
6. Lewis J, Quesenberry Jr C, Ferrara A, Vaughn D, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone. *Diabetes Care* 2011;34:91-922.
7. 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;34:1369-1371.
8. D. L. Fienstein et al. *J Bioc Pharmaco* 2005;70:177-188
9. V.Panikar, N. Kale, SS Hoskote, S Joshi. Relationship between pioglitazone dose and weight gain and glycemic control in newly diagnosed type 2 diabetics. Presented at the 2009 IDF conference, Montreal