Point of View

Pioglitazone – Where do we Stand in India ?

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The horizon of therapeutic management of type 2 diabetes mellitus is possibly shrinking at a faster pace than it is expanding. Many new drugs introduced in the last decade face an uncertain future due to safety issues, not withstanding their proven clinical effectiveness. With the advent of thiazolidinediones, (also called "GLITAZONES"). The management of type 2 diabetes mellitus took a giant leap forward as this is the only class of drugs, other than biguanides, to address the main pathophysiological defect in type 2 diabetes i.e insulin resistance. Glitazones have beneficial effects beyond their blood glucose lowering properties.[1] However, right from the beginning, this class of drugs was mired in controversy because of their side effect profile due to which most drugs in this class have gone off the therapeutic armamentarium at some stage or the other.

The first molecule of this class to see the light of day was Troglitazone which became an instant success, particularly in the US. However it had to be soon withdrawn from the market because of its hepatotoxicity.[2] Subsequently two molecules of the same class were launched namely Rosiglitazone and Pioglitazone. In view of the hepatotoxic effects of Troglitazone, the US FDA initially mandated regular monitoring of the liver function status when these two drugs were introduced.[3] It soon became apparent that they were virtually devoid of hepatotoxicity and hence the mandate of monitoring liver function was dropped. However, both rosiglitazone and pioglitazone had their own spectrum of side effects like weight gain, decrease in haematocrit values, edema, cardiac failure, fractures and possible worsening of diabetic macular edema.[4] Due to their remarkable efficacy in terms of glycemic control, they became popular and were widely used globally in spite of these side effects.

The ADOPT trial showed rosiglitazone to be a better alternative to metformin or glyburide as monotherapy in people with newly diagnosed diabetes on account of greater durability of the glucose lowering effect.[5] The DREAM trial showed that rosiglitazone prevented the risk of progression to type 2 diabetes mellitus by 72% and increased the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance.[6] However, a meta-analysis of 42 pooled studies by Nissen et al [7], first raised concerns regarding the increased incidence of myocardial infarction in patients receiving rosiglitazone. Although this was never conclusively proven, the media hype and subsequent studies suggesting that there could be a small increase in coronary artery disease rates, eventually led to a drastic decline in the use of this drug, culminating in it being banned in several countries including India.[8]

This left pioglitazone as the sole agent in the thiazolidinedione class. One of the largest trials conducted on pioglitazone, PROACTIVE showed that pioglitazone improved glycemic control and additionally suggested a possible cardio-protective effect.[9] The PERISCOPE trial also showed that pioglitazone was associated with improvement in CV risk factors and prevention of atherosclerosis progression compared to glimepiride.[10] In the CHICAGO trial, pioglitazone significantly slowed the progression of carotid intima-media thickness (CIMT) compared with glimepiride.[11] The PIPOD study also showed reduction in CIMT progression with pioglitazone.[12] Studies showing significant reduction in rates of restenosis and target vessel revascularization in percutaneous coronary intervention patients treated with pioglitazone provided further evidence for a vascular benefit.[13] The most recent trial, ACT NOW, showed that Pioglitazone, compared to placebo, reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% but was associated with significant weight gain and edema.[14]

However the bad luck with the glitazone group of drugs seems to have finally caught up with pioglitazone also. A link between pioglitazone and bladder cancer first appeared in preclinical studies but initial experimental studies suggested that this might be a rat-specific phenomenon.[15] Unfortunately this risk has now been reported in human studies also. This is an intriguing situation, because PPARγ agonists have also been shown to have anticancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation. Indeed PPARγ is currently considered a potential target for both chemoprevention and cancer therapy based on some preclinical studies.[16] However, other studies in rodents have shown that PPARγ agonists can potentiate tumorigenesis and can act as carcinogens. Therefore, TZDs like pioglitazone may increase, decrease or have a neutral effect on the risk of cancer or cancer progression in different species.[17]

In order to fully appreciate the significance of this issue, we must first review the available literature on the prevalence of bladder cancer in the general population. Bladder cancer is estimated to occur in 20 per 100,000 persons per year in the US and this prevalence is believed to be higher in people with diabetes. The incidence of bladder cancer is three times higher in men than in women[18]. More than 90% of bladder carcinomas are transitional cell carcinomas derived from the uroepithelium, about 6% to 8% are squamous cell carcinomas, and about 2%, adenocarcinomas.[19] Adenocarcinomas may be either of urachal origin or of nonurachal origin; the latter type is generally thought to arise from metaplasia of chronically irritated transitional epithelium.[20] Low risk bladder cancers do not impact the life expectancy of the patient. Conversely, high risk bladder cancers have the potential to metastasize and this could impact the life expectancy. The recent pioglitazone data does not highlight what kind of bladder cancers are increased among people suffering from diabetes and hence much more studies are needed in this regard.

A recent analysis published in Diabetes Care[21], reports on

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data on bladder cancer associated with antidiabetic drug use retrieved from the US FDA Adverse Event Reporting System (AERS). This showed an odds ratio > 1.0 for pioglitazone which is in agreement with preclinical and other clinical observations. Out of 37841 adverse events reported with the use of pioglitazone, 31 cases of bladder cancer (23 in men and 8 cases in women) were reported showing a reporting odds ratio (ROR) of 4.30, (95% confidence intervals: 2.82 – 6.52, p<0.001). However one of the serious limitations of AERS data is that the denominator from which these adverse events derived is unknown. Without this information, it is clearly not possible to come to any definite conclusions whether the risk of bladder cancer with pioglitazone reflects any excessive risk, over and above the risk reported in people with diabetes.

The Kaiser Permanente study in California, USA[22] included 1,93,099 patients aged ≥40 years of age at study entry. The median duration of therapy among pioglitazone-treated patients was 2 years (range 0.2-8.5 years). The results showed that after adjusting for age, sex, use of tobacco products, use of other categories of diabetes medications, and other risk factors, the risk of bladder cancer increased with increasing dose and duration of pioglitazone use. Patients who were on pioglitazone therapy for longer than 24 months, were found to have a 40% increased risk of bladder cancer (Hazard Ratio: 1.4; 95% CI 0.9 to 2.1). A positive correlation was also noted between the risk of bladder cancer and the duration of exposure and the cumulative dose of pioglitazone used. Based on these data, FDA calculated that duration of therapy with pioglitazone longer than 12 months was associated with 27.5 excess cases of bladder cancer per 100,000 person-years follow-up, compared to non- use of pioglitazone.

Another recent retrospective cohort study[23] using data from the French National Health Insurance Plan, included approximately 1.5 million patients with diabetes who were followed up to 4 years. The results showed that after adjusting for age, sex, and use of other anti-diabetic medications, there was a statistically significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents (HR 1.22; 95% CI 1.03 to 1.43). The results showed that the increased risk of bladder cancer was related to a cumulative dose of pioglitazone >28,000 mg (HR 1.75; 95% CI 1.22 to 2.5) and to exposures longer than 1 year (HR 1.34; 95% CI 1.02 to 1.75). A significant increase in risk was observed in males (HR 1.28; 95% CI 1.09 to 1.51), but not in females. France immediately suspended the use of pioglitazone and Germany also recommended not to start pioglitazone in new patients.

Based on the Kaiser Permanente study, the US FDA has issued a statement stating that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer and mandated that information about this risk be added to the Warnings and Precautions section of the label for pioglitazone-containing medicines. The US FDA has also asked to revise the patient medication guide for pioglitazone including information regarding the increased risk of bladder cancer. FDA has further recommended that healthcare professionals should not use pioglitazone in patients with active bladder cancer and to use it with caution in patients with a prior history of bladder cancer. Finally, the FDA has stated that additional information should be provided to patients stating that they should report to a physician if there are any symptoms of bladder cancer such as blood or red color in urine, urgent need to urinate or pain while urinating, pain in back or lower abdomen.[23]

In contrast, the European Medical Agency alert concludes that the benefit/risk balance remains positive in favour of Pioglitazone in a limited population of patients with type 2 diabetes and that the small increased risk of bladder cancer could be reduced by appropriate patient selection. However, this agency also recognizes the need for periodic review of the efficacy and safety of the individual patient's treatment. The agency's committee for Medicinal Products for Human Use (CHMP) concluded that although there is a small risk of bladder cancer with pioglitazone, overall its benefits continue to outweigh its risks in type 2 diabetes patients.[24]

Unfortunately none of this data is based on studies designed to specifically look for bladder cancer risk in patients treated with pioglitazone. Thus one cannot exclude the fact that the carcinogenesis may be due to other drugs used concomitantly with pioglitazone.

Where do we Stand with Regard to Pioglitazone in India?

There is no doubt at all regarding the therapeutic potential of the glitazone group of drugs. Both rosiglitazone and pioglitazone have been hugely successful in controlling the HbA1c levels in a large number of patients with type 2 diabetes. Insulin resistance is more common in Asian Indians[25,26] and hence glitazones have been very popular in India.

The correlation between pioglitazone and bladder cancer is seen with duration of the therapy more than 24 months and a cumulative dose of more than 28,000 mg which corresponds to an average daily dose of pioglitazone of about 40 mg/day. The doses used in US and Europe are 30-45 mg/day. In India, we generally do not use doses greater than 30 mg, which means, to achieve a cumulative dose of 28,000 mg, we would take longer and if we use low dose (7.5 mg) pioglitazone, it would take about 10 years. Indeed, low dose pioglitazone has of late become very popular in India due to its efficacy and lower frequency of side effects like weight gain and fluid retention. However, we do not know whether Indians are equally, more, or less, prone to risk of bladder cancer than Europeans.

Cardiovascular disease prevention often requires long term use of pharmaceutical intervention. The PROACTIVE data demonstrates that 11.3% of 2605 diabetes subjects on pioglitazone had a CV death, myocardial infarction, stroke or acute coronary syndrome (N= 294) compared to 13.9% of 2603 diabetes subjects not on pioglitazone who had a CV death, myocardial infarction, stroke or acute coronary syndrome (N= 361). Therefore, 66 fewer events in 2.8 years or 23 fewer events per year per approximately 5,000 diabetes subjects occurred in the pioglitazone arm. With respect to bladder cancer, it is expected that one diabetes subject out of 5,000 per year will get bladder cancer regardless of glucose lowering treatment. In view of pioglitazone's benefit in heart attack and stroke prevention, it would have to increase the risk of bladder cancer about 20 fold to offset its potential cardiovascular benefit. Probably, the agencies rendering judgment on pioglitazone are only considering its benefit on blood glucose control, as this is its only formal indication for the drug. If one includes prevention of CV events and diabetes, the benefit to risk ratio may be different.

Cancer as adverse effects of any drug is difficult to prove for several reasons. There is a time lag in development of cancer from the time of initial insult. Cancers have multifactorial etiologies including genetic interaction with a variety of offending agents. Sometimes they grow slowly and are diagnosed after a

considerable time has passed. Finally as pointed out, patients with diabetes are more prone to develop certain types of cancers. All these factors make it almost impossible to identify a particular drug as an initiating agent of a tumour, particularly when, during the same period, the patient could have been exposed to a variety of potentially carcinogenic drugs, chemicals and environmental factors.

However, given the possible risk of bladder cancer, physicians have to be extremely careful about using pioglitazone indiscriminately in the future. For those who are currently on the drug, the risk of bladder cancer has to be explained and wherever possible the drug should be withdrawn, particularly if there is a history of any cancer in the family. If the patient himself or herself has had cancer, the drug would definitely have to be withdrawn. One must realize that withdrawing pioglitazone could result in increased doses of other glucose lowering agents (eg. metformin) or adding alternative drugs eg. sulphonylureas or DPP IV inhibitors which may or may not work in that given patient. It is also likely that a large number of patients in whom pioglitazone is withdrawn would have to be ultimately treated with insulin. However, as physicians, our primary responsibility is the safety of our patients and whenever the benefit to risk ratio is low, the drug should be withdrawn.

In conclusion, we require more robust data on the risk of bladder cancer with pioglitazone and Indian studies are clearly needed. Till that time, we may continue the use of this drug as a second or third line glucose lowering agent. In all such cases, the patient should be adequately informed about this adverse effect and drug should be used in as small a dose as possible, with careful monitoring and follow up.

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