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REVIEW ARTICLE

Pioglitazone and Bladder Cancer in India, a Real Threat or Man-Made Fiasco: A Review

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Abstract: ***Pioglitazone is an oral anti-diabetic agent that, in the presence of insulin resistance, increases hepatic and peripheral insulin sensitivity, thereby inhibiting hepatic gluconeogenesis and increasing peripheral and splanchnic glucose uptake. Pioglitazone is generally well tolerated; however some preclinical in vivo studies and limited human data suggest a possible increased risk of bladder cancer with pioglitazone therapy. Therefore, we sought to perform a systematic review to evaluate the magnitude of this association and the quality of the supporting evidence. Based on the available data, pioglitazone still appeared to be an important option either as monotherapy or in combination, considering its efficacy, safety and cost especially among Indians diabetic patients. Good glycemic control is more important than routine cystoscopy among the pioglitazone users, although patients complaining of urinary symptoms must undergo detailed investigations for bladder cancer. Of course, individuals with any bladder malignancy, stand as a contraindication to initiate pioglitazone.***

At the end of the analysis, we felt this issue of bladder cancer has been over highlighted. As long as pioglitazone is prescribed in a judicious manner, the therapeutic benefits clearly overweigh the risk associated with it.

Keywords: ***Pioglitazone, oral anti-diabetic agent, bladder cancer, glycemic control.***

Introduction

The overwhelming incidence of diabetes has now become a known fact to every common man. Therefore things related to it, especially a controversy create a big buzz in the society. Few years back, when a relatively uncommon form of cancer was found to be associated with the use of a fairly common oral anti diabetic agent pioglitazone, physicians around the world were surprised.

History of Glitazones

For quite some time, Glitazones have been frequently used to treat type 2 Diabetes mellitus by the physicians around

the world. Pharmacologically they belong to the group Thiazolidinedione's (TZD) under oral anti diabetic agents. Historically ciglitazone was the first ever TZD; however the poor safety profile prevented it to be clinically used. Troglitazone, pioglitazone, englitazone, darglitazone and rosiglitazone are the other agents which surfaced in the later years. In January 1997, troglitazone got the approval for commercial use only for a short period of time before being withdrawn from the market in 2000 due to its hepatotoxicity.[1,2]

Similarly rosiglitazone was also banned in several countries because of the risk of small increase of coronary artery disease as reported by few studies.[2,3]

Pioglitazone received the US approval on 15th July1999 and in the European Union on 13th October 2000 and since then it has been successfully used to achieve glycemic control all over the world.[4]

Mechanism of Action

The pharmacological effect of pioglitazone as an oral anti diabetic agent has been extensively studied. Inside adipocytes, glitazones bind to a nuclear receptor PPAR-γ (Peroxisome proliferator-activated receptor-gamma) which in turn binds to the 9-cis retinoic acid receptor (Retinoid X receptor/ RXR) to form a heterodimer. This results in increased transcription of transporters and enzymes responsible for fatty acid uptake, leading to lipid deposition or lipogenesis in the adipocytes. Consequently there is a reduction of non-esterified fatty acid and triglycerides as energy sources which ultimately promotes glucose uptake and thus controls hyperglycemia.[5]

Besides this, TZDs also improves the glucose utilization by directly enhancing the transcription of GLUT-4 transporter. Reduction in the insulin resistance is one of the most important effects exerted by the TZDs which may be attributable to the increase in adiponectin levels and reduction in adipocyte tumor necrosis factor-alpha (TNF-α) and resist in production.[5,6]

PPAR-γ is also expressed in macrophages, endothelial cells and vascular smooth muscles where it controls the process of atherosclerosis by regulating the lipid metabolism, vascular inflammation and proliferation.[7]

After oral administration the drug is highly protein bound and primarily metabolized by CYP2C8 and to a lesser extent by CYP3A4.[4,8]

Besides regulating carbohydrate metabolism, PPAR γ has been a potential target for both chemoprevention and cancer therapy. Because of its anti-proliferative, pro-apoptotic and differentiation promoting activities, PPAR γ has been intensively evaluated as a target for anti-cancer therapy in preclinical models.However, PPAR γ has been reported to act both as a promoter and suppressor of neoplasia, and the role of PPAR γ activating ligands as well as antagonists in therapy remains controversial. Thiazolidinediones also exhibited anti-angiogenic activity, independent of the PPAR- γ effect.[9]

Therapeutic Success in type 2 Diabetes Mellitus

As monotherapy

Pioglitazone as monotherapy can improve the glycated hemoglobin levels (HbA1c) and is useful if metformin is contraindicated or not tolerated.[10,11]

And it can reduce the HbA1c between -0.8% to -1.05% over a period of 12-26 weeks time.[10,4]

When compared to metformin, the HbA1c lowering was in the range of - 1.3% to -1.6% by pioglitazone as monotherapy.[4]

As combination therapy

As a dual oral therapy pioglitazone is often combined with metformin or sulfonylureas to achieve a better glycemic control. These combinations were found to be significantly more effective than the monotherapy in terms of reduction of blood glucose and improvement of HbA1c levels.[4]

Addition of 15-30mg of pioglitazone daily to the existing oral anti diabetic agents has decreased the HbA1c values by 0.64% and 1.26%.[10]

HbA1c reduction was as high as 1.5% in a study which used triple drug combination of pioglitazone, metformin and insulin secretagogues.[4]

Another study compared human insulin(70/30 premix) plus 500mg sustained-release metformin given twice daily versus a triple oral fixed dose diabetes polypill containing 1-2mg glimepiride, 500mg sustained-release metformin and 15mg of pioglitazone administered once a day. The triple drug combination not only lowered HbA1c (-1.33% versus -0.83%; p= 0.059), but also the number of subjects achieving a decrease of HbA1c of more than 1% were significantly more (72.5% versus 22%; p=0.0001). The fasting and postprandial sugar levels were reduced equally by both regimens (p=0.05). The Insulin regimen caused more weight gain which was however, non significant (2.69 kg versus 0.92 kg; p= 0.223). Tolerability of the triple drug regimen was also better.[12]

Pioglitazone has also exhibited impressive result when used with insulin therapy in type 2 diabetic patients.

Addition of 30mg and 45mg of pioglitazone to the patients who are poorly controlled with insulin resulted in a fall of HbA1c levels by 1.17% and 1.45% respectively over a period of 24 weeks.[4]

An Indian study was conducted involving patients aged 40-70 years, who were poorly controlled by glibenclamide, metformin and insulin for over 3months duration. Pioglitazone was given to them for 6 months at a fixed dose of 30mg daily, which resulted in significant reduction of both fasting glucose and HbA1c levels. Apart from this, insulin therapy could be completely halted in 42.1% of the patients and the addition of pioglitazone led to insulin sparing in 56.32%.[13]

Diabetes prevention

An open label follow up study called PIPOD, has shown that pioglitazone arrested the pancreatic beta cell dysfunction and provided stability to them.[14]

To evaluate if pioglitazone can reduce the risk of conversion of impaired glucose tolerance (IGT) to frank type 2 diabetes, a randomized placebo controlled trail was conducted involving 602 adult patient with IGT. Surprisingly, pioglitazone has reduced the risk of development of frank type 2 diabetes by 72% in comparison to placebo but at the cost of significant weight gain and edema.[15]

Cardiovascular benefits

Beyond providing the glycemic control, pioglitazone has also exhibited cardiovascular benefits among the diabetic patients. The prospective pioglitazone clinical trial in macrovascular events (PRO active) study is one such which supports the fact. It was a prospective randomized control study, which was conducted on 5328 patients suffering from type 2 diabetes, who were assigned to oral pioglitazone (n=2605) or matching placebo (n=2633), to be taken in addition to the other anti-diabetic medications and other medications. At the end of the trial, pioglitazone non significantly reduced the risk of composite primary end points like 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.[16]

Further analysis of the above study revealed that subgroup of previous MI patients has also shown a reduction in fatal and non-fatal MI during the course of the treatment (n=2445, HR 0.72, 95% CI [0.52-0.99], p= 0.045; NNT =51, 95% CI).[16]

A similar analysis of the subgroup with previous history of stroke has shown a reduction in both fatal and non-fatal stroke after the pioglitazone therapy (n=984, HR=0.53, 95% CI [0.34-0.85], p=0.0085; NNT=21, 95% CI).[16]

A large meta analysis involving 84 published and 10 unpublished studies and excluding PRO active study, comparing pioglitazone and placebo, has shown a reduction of all cause mortality with pioglitazone (Odds ratio 0.30, 95% CI [0.14-0.63], p<0.05).[17]

Another meta-analysis with 16390 patients has come up with a reduction of primary composite end points like death, MI or stroke with pioglitazone therapy in comparison with control.[18]

The protective effect of pioglitazone on cardiovascular system was also observed in other trials based on the surrogate or laboratory endpoints. Carotid intima-media thickness in atherosclerosis using pioglitazone trial (CHICAGO) has shown a significant slowing of the progression of carotid intima-media thickness (CIMT) by pioglitazone in comparison with glimepiride over 18 months treatment.[19]

According to the pioglitazone effect on regression of intravascular sonographic coronary obstruction prospective evaluation (PERISCOPE) trial, pioglitazone was associated with improvement in cardiovascular risk factors and prevention of atherosclerosis progression in comparison with glimepiride.[20]

Another study was conducted with 22 diabetic patients with left ventricular ejection fraction more than 40%. They received 15mg of daily pioglitazone for 12weeks besides the other anti diabetic treatment. Here both fasting blood glucose and HbA1c were significantly reduced by pioglitazone. Although the low and high density lipoproteins values were unaffected, there was a significant decrease in the triglyceride levels at the end of the study.[21]

Earlier data proved the efficacy of pioglitazone in the reduction of urinary albumin excretion (UAE) and urinary ET-1(Endothelin) concentration in NIDDM patients with microalbuminuria, when given at 30mg daily dose.[22]

Similar therapeutic benefit was obtained by the addition of pioglitazone to the RAAS inhibitors in terms of decrease in urinary albumin excretion in type 2 diabetic patients with hypertension and microalbuminuria.[23]

Other effects

Non alcoholic fatty liver disease (NAFLD) is an emerging health problem. Many studies so far, have evaluated the effect of oral insulin sensitizers in NAFLD.[24] Improvements in terms of both biochemical and histological

parameters like fibrosis have been observed in one such recent randomized placebo controlled clinical trial after pioglitazone therapy for 12 months in a with 74 non diabetic patients with histologically proven NASH (Non alcoholic steato hepatitis).[25]

The Cancer Issue

Encouraging results were found from preclinical studies, where PPAR γ agonists showed anticancer effect by inhibiting growth and inducing apoptosis and cell differentiation .[26]Unfortunately, these in vitro and preclinical data did not reflect in clinical studies with colorectal and prostatic carcinoma. In fact, pioglitazone has actually shown tumor inducing effect in murine models.[27]Another preclinical study with rodents has shown that PPAR γagonists can actually potentiate tumor genesis. Hence, they concluded that Thiazolidinediones (TZDs) may increase, decrease, or have a neutral effect on the risk of cancer or cancer progression in humans.[28]

Not much of human data associating cancer risk with pioglitazone was available then, except for a meta-analysis with rosiglitazone which was inconclusive. And these trials measured only the short term exposure of the drug up to 6 years due to the recent advent of the molecule at that point of time.[29]

Since then, there has been some debate on this issue and significant literatures have already been published. Recently, the matter again flared up when US FDA Adverse Event Reporting System (AERS) revealed 31 new cases of bladder cancer (23 in men and 8 cases in women) out of 37841 adverse events reported with the use of pioglitazone, showing a reporting odds ratio (ROR) of 4.30,(95% confidence intervals: 2.82 – 6.52, $p<0.001$).[30]

Later, the Kaiser Permanente study in California, involving 1, 93,099 patients showed a shocking 40% higher risk of development of bladder cancer among the patients who were on Pioglitazone therapy for longer than 24months (Hazard Ratio: 1.4; 95% CI 0.9 to 2.1) after adjusting for age, sex, use of tobacco products, use of other categories of diabetes medications, and other risk factors.[31]

Based on the above report, FDA quickly estimated 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.[32] Subsequently, this information appeared in the drug label containing pioglitazone in USA. The FDA also 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.[33]

Meanwhile in Europe, a French retrospective cohort study also came up with a statistically significant increase 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) that after adjusting for age, sex, and use of other anti-diabetic medications. A male predominance among the affected individuals was also observed (HR 1.28; 95% CI 1.09 to 1.51), similar to the USA based observation. This study also 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). As a result, pioglitazone was immediately banned in France, whereas Germany advised not to start the drug in new patients. [34]

However, the European Medical Agency concluded that the benefits of pioglitazone in type 2 Diabetic patients overweighed the risk of bladder cancer, which can be minimized by appropriate patient selection and periodic review.[35]

Since then, quite a few studies have attempted to estimate the exact amount of risk attached to the use pioglitazone. A recent meta-analysis from 17 different studies showed a modest risk of bladder cancer among the pioglitazone users (RR: 1.20; 95% CI: 1.07–1.34 from six studies), although there was no overall risk of cancer among the thiazolidinedione users (RR: 0.96; 95% CI: 0.91–1.01). The RRs of bladder cancer were higher for longer duration (RR: 1.42 for >2 years) and higher cumulative dose of pioglitazone (RR: 1.64 for >28,000 mg).[36]

There was not much of available data from Asia, until a recent multicentre retrospective cohort study was conducted in Korea, involving the Diabetes patients who are on 15mg daily dose of pioglitazone. The study, however failed to exclude the possibility of bladder cancer among the pioglitazone users for more than 6 months duration.[37]

Indian Scenario

Back in India which harbors a major chunk of global diabetes population, eight new cases (seven male and one female) of bladder cancer among the pioglitazone users have already surfaced, out of which one even expired in November 2011 due to metastasis.[38] Surprisingly, these patients received the drug at a lower dose than that of the patients from USA, making the safety profile to further

dip among Indians. These facts were enough to make the DCGI skeptical and they eventually put a suspension on the manufacture, commercial sale and distribution of pioglitazone on 18th June 2013, only to revoke it after a month and half (31st July) after issuing a warning.[39]

Discussion

Now let us dig deeper into the issue. Few of the Indian researchers have already expressed their views on this emergent issue of bladder cancer associated with pioglitazone. They feel, in the first place, none of those initial studies[30, 31] was specifically designed to look for bladder cancer risk with pioglitazone and therefore patients were not thoroughly screened for the risk of bladder malignancy before starting the drug. Additionally, the studies were neither prospective, nor well balanced in nature. So, it is not wise to extrapolate the findings in general population.[40]

Secondly, diabetes itself is a precancerous condition and the risk of development of certain cancers involving pancreas, liver, endometrium, breast, colon, rectum and urinary bladder was found to be higher among the diabetic population.[41]

Chronic low grade inflammation of diabetes and the effect of hyperglycemia induced oxidative stress, accumulation of advanced glycation end products on proteins and other macromolecule are considered to be responsible for this malignant transformation.[42, 43]

Insulin resistance and hyperinsulinemia (either endogenous due to insulin resistance or induced by administration of exogenous insulin formulations) are independent risk factors for the development of malignancy in type 2 diabetes mellitus.[44]

Moreover, type 2 diabetes and cancer share several common potential risk factors (e.g., aging, sex, obesity, physical activity, diet, alcohol, and smoking) and cancer takes substantial amount to develop form the initial insult. Therefore, it is almost impossible to prove malignancy as an adverse effect of a drug particularly when, during the same period the patient could have been exposed to a variety of potentially carcinogenic factors.[44, 32]

It was estimated that more than 28000mg of cumulative doses of pioglitazone for more than 24months therapy, may link the drug with bladder cancer, which corresponds to about 40mg/ day dosage. In India daily dose of more than 30mg is quite rare, unlike USA and Europe, where the usual dose ranges from 30 to 45mg/day. Going at that pace, an Indian would require almost 10years to reach a cumulative dose of 28000mg, if he is on low dose (7.5mg/ day) pioglitazone.[32]

Again, withdrawing pioglitazone may demand higher doses of other oral anti diabetic agents (Metformin, Sulfonylureas) or even addition of alternative agents like DPP IV inhibitors or GLP-1 analogues, which are not only expensive, but have unknown long term safety records. It is also likely that a large number of such patients will ultimately require insulin therapy.[32]

In India the annual median expenditure by the patients on diabetes care us Rs 10000 in urban and Rs 6300 in rural areas. Low income group spends nearly 25-30% of their annual income on diabetes care. Pioglitazone is still economical and causes less hypoglycemia, which reduces the burden of frequent glycemic monitoring and thus reduces the health care cost.[45]

On the basis of PROactive study data; two more pharmaco-economic evaluations were performed in US and UK. A long term cost effectiveness study from US has shown that addition of pioglitazone to the existing anti diabetic therapy was associated with increased life expectancy (0.237 life years) and quality adjusted life expectancy (QALE) [0.116QALYs] versus placebo. Total lifetime cost was slightly higher with pioglitazone than placebo ($272694 versus $265390). The incremental cost effectiveness ratio for pioglitazone versus placebo was $44105 per QALY gained. Again probabilistic sensitivity analysis indicated a 55% likelihood of pioglitazone being cost effective in the US, with a willingness to pay of $50000 per QALY gained.[46]

A similar study was performed in UK from the data of PROactive clinical study to analyze the cost effectiveness of the addition of pioglitazone to existing treatment regimens in patients with Type 2 diabetes with a history of macrovascular disease who are at high risk of further cardiovascular events. The result indicated that the incremental cost-effectiveness ratio (ICER) of pioglitazone vs. placebo was pounds 4060 per QALY gained. The cost-effectiveness acceptability curve showed there was an 84.3% likelihood that pioglitazone would be considered cost-effective and represents good value for money by currently accepted standards in the UK using a willingness-to-pay threshold of pounds 30 000 per QALY gained.[47]

While all those were happening, there was not much of Indian data available to analyze. Finally, a study comprising of 958 Indian patients, aged between 18 to 60 years with poorly controlled type 2 diabetes gave us some clarity regarding the risk benefit of pioglitazone among Indian diabetic population. According to the result,

pioglitazone in the dose range of 7.5mg to 30mg per day reduced FBG, PPBG and HbA1c both as monotherapy and in combination with other oral anti diabetic agents over a period of two years. HbA1c reduction was as high as 2.6% compared to placebo with pioglitazone monotherapy, while the same was 1.58% in case of combination therapy in a dose-response fashion. And the improvements of glycemic parameters were found in every visit during the study duration. Improvement of both hepatic and peripheral insulin sensitivity was also evident despite the weight gaining effect of the drug. In the same study, urinalysis of all the patients across all the dosage studied, showed no significant change from baseline in terms of urinary pH, proteinuria, pyuria and hematuria, indicating no link between pioglitazone and bladder related abnormality. Based on his observation, the author advocated the use pioglitazone as a very good 'insulin sensitizer' in the dose range of 7.5-15 mg/day among Indians.[48]

This observation is similar to a propensity score matched analysis conducted just a few years back in UK, which also came up with no statistical increase of bladder cancer among pioglitazone users compared to other oral anti diabetic agents. The event rates were 76.0 (95% CI 55.2, 99.8) per 100 000 person-years for the pioglitazone treatment group and 71.3 (95% CI 51.1, 91.5) per 100 000 person years for the other oral hypoglycemic drugs treatment group. The population attributable fraction suggests that only 1% of bladder cancer could due to use of pioglitazone.[49]

South Asians consume high fat, high calorie diet (HFHC) and they are more prone to become diabetic at a younger age and with low BMI compared to Caucasians.[50]

The "Asian Indian Phenotype" is a unique group with certain clinical and biochemical abnormalities like increased insulin resistance, higher waist circumference with lower BMI, lower adiponectin and higher high sensitive C-reactive protein (hsCRP) levels. The risk of development of diabetes and coronary artery disease is much higher among them.[51] Therefore, pioglitazone turns out to be one of the ideal choices of oral agent to combat diabetes mellitus in this part of the world.

A comparative clinical study was conducted in Chennai to evaluate the effect of pioglitazone, rosiglitazone with glibenclamide in the patients with type 2 diabetes and associated dyslipidemia. Both the glitazones showed favorable lipid lowering effect besides their anti-hyperglycemic role. Moreover, pioglitazone has also improved the HDL levels in such patients during the course of the study. Therefore TZDs can be a very good option in the setting of hyperglycemia with dyslipidemia and thereby prevention of cardiovascular mortality.[52]

Another retrospective cohort study from a cancer hospital in Chennai tried to evaluate the risk of bladder cancer among the users of antidiabetic agents. Surprisingly the number of patients with bladder cancer was the lowest with pioglitazone (0.39%) in comparison with other agents like metformin, DPP4 inhibitors, sulfonyl ureas and insulin.[53]

There is also an ongoing study at Chandigarh to analyze the risk of bladder malignancy among the pioglitazone users (PROBE-PIO). 6107 type 2 diabetes mellitus patients have been enrolled from July 2013 and it is expected to be over by August 2015.[54]

A useful guideline pertaining to bladder cancer from a large private tertiary care hospital from Gurgaon has already been published. In their practice, pioglitazone is prescribed as a fourth oral anti-diabetic agent only after metformin, incretin based therapy and sulfonylureas. However, pioglitazone can come earlier depending on the side effects, contraindications or economic reasons of the first three agents. The daily dose is typically set at 15mg and more than that is usually avoided. However, lower doses like 7.5mg are not administered.

Quite wisely, they have refrained from using the term "cancer" while discussing the therapy with the patient, as the word 'cancer' carries a significant fear factor which may lead to complete refusal of therapy. And this, if future may be an important challenge for the physicians to initiate pioglitazone.

To be on the safe side, the hospital does not advocate pioglitazone in case of pre- existing bladder cancer and would discontinue if the symptoms of bladder cancer appear. According to Ambrish Mithal et al, their prescription pattern so far remained unaffected by bladder cancer. And he concluded that, despite having proven anti-hyperglycemic efficacy and low cost, pioglitazone should be prescribed only to a limited number of patients who actually require it, rather than using it as a standard therapy, which is a common practice in our country.[55]

Let us not forget the role the Indian drug regulatory authority has played during the process. According to Arif Hashmi, the Indian media widely quoted the ban of pioglitazone in France and Germany, which has heavily influenced the Indian drug regulatory authority to suspend the molecule. He also thinks, the decision by DCGI reflected a lack of understanding of the full impact of non-availability of this drug on the Indian patients.[56]

The same article also highlighted certain technical

flaws in the process of suspension of the molecule. The author has questioned the decision of DCGI to go ahead without any due recommendation from the Drug Technical Advisory Board (DTAB), which is empowered to takes up such issues. CDSCO website provides minutes of the meeting of Analgin, another drug suspended along with pioglitazone but surprisingly, does not show any discussion on pioglitazone. He also pointed out that, there have been no reports indicating suspicious signals for pioglitazone to the Pharmaco-vigilance Program of India (PVPI) prior to this ban.

Besides this, the popular press has described this incident as a case of conflict of interest, to promote the expensive gliptins group of oral anti-diabetic agents by smearing pioglitazone. Therefore the author rightly feels that the whole incident deserves a fair investigation especially when the molecule has been used globally for nearly two decades and extremely valuable for Asian-Indian diabetic population.[56]

We feel pioglitazone's therapeutic indications still remain same in India like any other parts of the world. Depending on the requirement of the patient, it has got ample potential both as a monotherapy and combination therapy with other oral anti-diabetic drugs like metformin, sulfonylurea and gliptins in the treatment of type 2 diabetes mellitus. However, a lower dose of pioglitazone (7.5-15mg per day) may be preferred among the Indians like many other countries.[57]

Precautions and monitoring of the pioglitazone therapy are just as important as any other drugs. Side effects like fluid retention leading to congestive cardiac failure, weight gain, dose related macular edema and risk of non vertebral fractures in females have been associated with the drug.

It should not be used in NYHA Class III or IV failure cases. Pregnancy remains another contraindication as well.

Regarding bladder malignancy issue, all patients must be investigated thoroughly for any evidences of bladder cancer prior to the therapy. Patients, who are already suffering from bladder malignancy, are certainly not suitable candidates for pioglitazone therapy.

At this point we feel routine investigation to rule out bladder cancer is not mandatory for all the patients who are on pioglitazone. A cystoscopy every three to four months may not be a feasible option for many Indian patients. Rather an adequate glycemic control can be more valuable, as persistent hyperglycemia itself predisposes to malignancy. Reduction of other modifiable risk factors for bladder cancer like smoking and obesity can be extremely beneficial in such patients.

However, the drug must be immediately withdrawn in case of any suspicious change of laboratory markers towards bladder malignancy or anyone develops symptoms like macroscopic hematuria, dysuria or urinary urgency during the course of therapy. And such situation demands a thorough investigation and subsequent treatment if required, without any delay.

One must also understand that on ethical ground it will never be possible to design a clinical trial, which would specifically quantify the risk of development of cancer associated with a drug. Therefore, the only option is to count on the data obtained from the clinical studies that are not exactly designed to address the issue. Perhaps, a well-planned epidemiological study or strict pharmacovigilance program hold the key to this answer in future.

Conclusion

Although there has been some concern regarding the development of bladder cancer among the pioglitazone users, robust supportive data, both global and Indian are still lacking. Literatures are also suggesting that the issue has been over-highlighted. At the same time, the molecule's efficacy as an anti-diabetic agent with additional cardiovascular benefits has been irrefutable for nearly two decades. Therefore, in a country like India with high prevalence of insulin resistance, pioglitazone continues to remain a good choice to treat type 2 diabetes mellitus, both as monotherapy and in combination as long as one maintains rationality. However, considering the possible risk of bladder cancer, all patients must be assessed before initiating pioglitazone and it is better to avoid the drug in patients with pre-existing bladder cancer. A detail investigation is only necessary if a patient develops urinary symptoms, rather than doing it on a routine basis for all those who are on pioglitazone.

In near future more studies are expected to come up, which may provide us further clarity about the issue. Since the molecule has got time-tested substantial clinical benefits, we believe, the risk of bladder malignancy is unlikely to surpass them.

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"Work out your own salvation. Do not depend on others."

— Buddha