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ORIGINAL ARTICLE

Pioglitazone - Current status in the management of Type 2 Diabetes patients in India

Hiren Prajapati

Intas Pharmaceuticals Limited, Gujarat, India

Abstract: Diabetes is a major public health issue worldwide which is approaching epidemic proportions globally, including India. Among the proven pathophysiological factors for the development of type 2 diabetes, insulin resistance is the most common among Indian type 2 diabetes. Pioglitazone is currently most commonly prescribed either alone or in combination with other oral anti -hyperglycemic agents that target insulin resistance and improve insulin sensitivity among type 2 diabetes. The biggest controversy with pioglitazone for bladder cancer is over now. 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. Dose dependent cumulative cancer by pioglitazone is also not possible in Indian patients because of low dose, i.e., 30 mg/day as a single dose is used unlike other countries 40 mg/day. To balance the pros and cons of pioglitazone use in Indian type 2 diabetes, the most suitable dose should be < 15 mg/day to gain significant glycemic control as determined by HbA1c along with better safety profile compared to higher dose prescription practice in Western countries. Current Indian data have been analyzed in this review article and it has been revealed that pioglitazone in lower dose of **7.5 mg**/day offers similar HbA1c reduction property as moderate dose of 30 mg/day pioglitazone with lesser incidence of side effects. Therefore, to continue the benefits of pioglitazone in type 2 diabetes, prescription of low dose of pioglitazone is emerging trend in India.

Keywords: Diabetes; pioglitazone; insulin resistance; bladder cancer; HbA1c

1. Diabetes – A global health care issue

Diabetes is a growing global problem with 424.9 million patients suffering from diabetes worldwide. India has the second highest number of people with diabetes which is at 72.9 million, next only to China - the diabetes capital in the world which has about 114.4 million. By 2045, it is projected that India will have 134.3 million people with diabetes and it will overtake China which will have 119.8 million persons with diabetes. [1]According to the Centers for Disease Control and Prevention (CDC), the increasing prevalence of type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes in adults. [2]Type 2 diabetes is a heterogeneous disorder characterized by impaired insulin secretion, reduced peripheral insulin action, and increased hepatic glucose production, all defects being present in variable proportions in different individuals.[3]

2. Insulin resistance and its targets

Epidemiological data link type 2 diabetes with obesity[4-7], and a causal relationship between insulin resistance and obesity has been derived from classical studies in which lean individuals with no previous history of obesity or diabetes became insulin resistant upon experimental overnutrition[8]. These facts strengthen the great importance of understanding the physiological basis for insulin resistance in type 2 diabetes. Insulin resistance is also linked to a wide array of other pathophysiologic sequelae including hypertension, hyperlipidemia, atherosclerosis (i.e., the metabolic syn-drome, or syndrome X), and polycystic ovarian disease. [9]Thus, Insulin resistance is not only the most powerful

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predictor of future development of type 2 diabetes but also a therapeutic target once type 2 diabetes is diagnosed. There are few oral anti hyperglycemic agents available like biguanides including metformin and thiazolidinediones including pioglitazone and rosiglitazone which strongly target the insulin resistance and improve insulin sensitivity. Among thiazolidinediones, pioglitazone is currently most commonly prescribed either alone or in combination with other oral anti -hyperglycemic agents for the management of type 2 diabetes in India.[10-12]

3. Pioglitazone

Pioglitazone is a thiazolidinedione, a class of antidiabetic drugs that exert their action by binding to the peroxisome proliferator-activated receptor gamma (PPAR-Y). PPAR receptors are found in insulin signaling tissues like adipose tissue, skeletal muscle, and liver. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. [13]It was approved by the US Food and Drug Administration (FDA) in 1999 [13] and European Medicines Agency (EMA) in 2000 [14] for the treatment of type 2 diabetes as monotherapy or as dual or triple combination with metformin, sulfonylurea, or insulin. It is known to reduce HbA1c significantly with an antihyperglycemic effect similar to that of metformin and sulfonylureas[15–17]. The recommended starting dose is 15 mg or 30 mg once daily. The dose can be titrated in increments of 15 mg up to a maximum of 45 mg once daily based on glycemic response.[13]

4. The biggest controversy with pioglitazone

Recently, pioglitazone was caught under bladder cancer controversy. In June 18, 2013, the Indian government suspended the popular anti-diabetic drug pioglitazone, over safety concerns only to revoke the suspension on July 31, 2013. [18]While the oral hypoglycemic controversial drug, which has been linked to urinary bladder cancer, is back on the Indian market with warnings. Though pioglitazone produces urinary bladder cancer in diabetic patients, a numerous beneficial positive characters with pioglitazone will support the need and continuous use of this safe drug in India for diabetic patients instead of be banned until alternative available. Pioglitazone figures as an acceptable oral anti diabetic drug in all international guidelines and recommendations. There are complicated and controversial aspects against pioglitazone and its urinary bladder cancer.

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, While in India pioglitazone does not use 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 [19] it would take 10 years. Dose dependent cumulative cancer by pioglitazone also not possible in Indian patients because of low dose, i.e., 30 mg/day as a single dose is used unlike other countries 40 mg/day.

5. Pros and cons of pioglitazone

There are pros and cons of pioglitazone for the management of type 2 diabetes patients as mentioned in figure 1.[20]

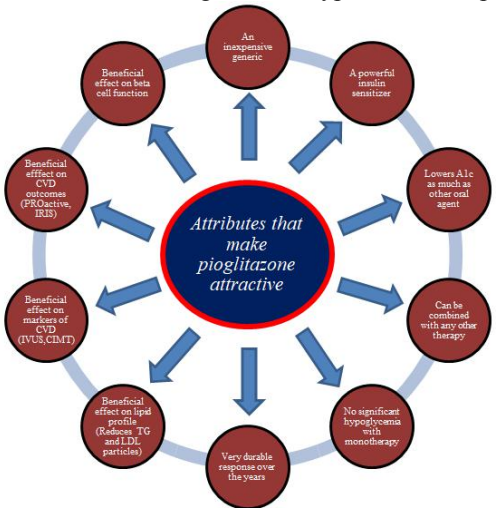

Figure 1, A; Pros of pioglitazone of pioglitazone for the type 2 diabetes management.

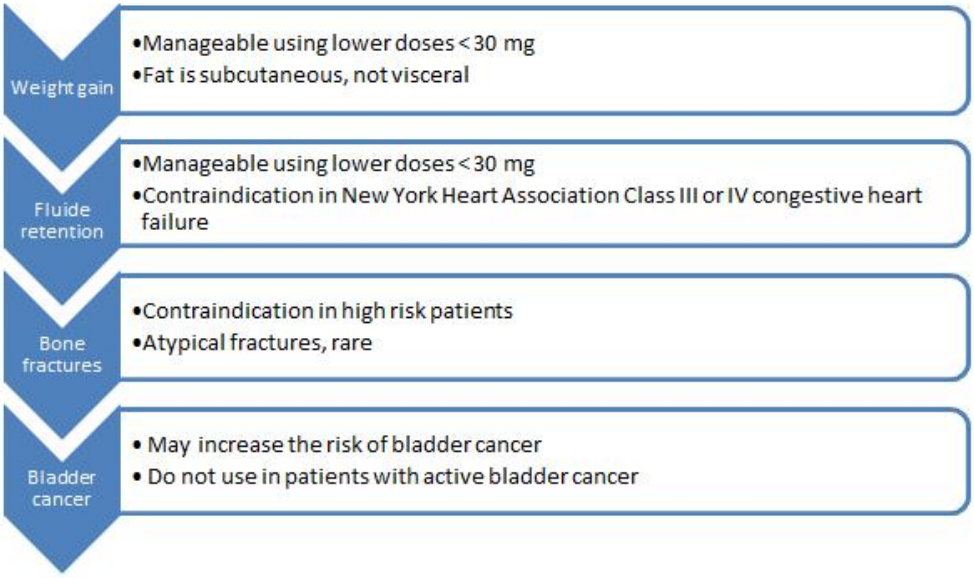

Figure 1, B; Cons of Pioglitazone of pioglitazone for the type 2 diabetes management.

In India, probably due to lower dose, lower background incidence of bladder cancer and smaller sample size in epidemiological studies, association of bladder cancer with pioglitazone was not found to be significant. [21]Therefore, for the utilization of pioglitazone among Indians, the most suitable dose should be < 15 mg/day to gain significant glycemic control as determined by HbA1c along with better safety profile compared to higher dose prescription practice in Western countries. Even 2017 American Association of Clinical Endocrinologists and American College of Endocrinology AACE/ACE guidelines on diabetes management also recommended the use of moderate dose (e.g., ≤30 mg) of pioglitazone to mitigate side effects like weight gain, increased bone fracture risk in postmenopausal women and elderly men, and elevated risk for chronic edema or heart failure.[22]

6. Significance of low dose of pioglitazone

Efficacy and safety of low (7.5 mg/day), medium (15 mg/day) and high (30 mg/day) dose Pioglitazone therapy were mentioned in Table 1.

Table 1 shows efficacy and safety of low, medium and high dose of Pioglitazone among type 2 diabetes patients.

Study conducted by author (Year)	**Sample size of patients(n)**	**Duration of study**	**Parameter**	**7.5 mg**	**15 mg**	**30 mg**	**P value#**
Panikar *et al* [2015] 23	237	24 weeks	Efficacy HbA1c (%)	- 1.24	- 1.18	- 1.25	0.813
			Safety Body weight (kg)	+0.88*	+1.62*	+2.72*	<0.001
Majima *et al* [2006]24	95	24 weeks	Efficacy HbA1c (%)	-0.61*	-0.69*		Non-significant
			Safety 1. Body weight (kg) 2. Pedal oedema	+1.14 2/54 (3.7%)	+2.79 11/41 (26.8%)		<0.0001
			Pedal				

Adachi *et al* [2017]25	40	8 weeks	Efficacy HbA1c (%)	-0.8**	-0.7**		Non-significant
			Safety Body weight (kg)	-1.0	+0.9		Significant
Rajagopalan *et al* [2015] 26	90	12 weeks	Efficacy HbA1c (%)	-0.5*	-0.6*	-0.7*	p=0.68
			Safety 1. Body weight (kg) 2. Body fat (%)	+0.2 + 0.1	+0.9* +0.8*	+1.9* +1.2*	Significant

*P < 0.05 and **P < 0.1 and vs. baseline, respectively

#P value refers to the difference between groups.

7. Key points from table

7.1 Pioglitazone 7.5 mg/day as monotherapy or as add on therapy seems as efficacious as pioglitazone 15mg/day and 30 mg/day as monotherapy or as add on therapy in terms of improving glycemic control as determined by HbA1c.

7.2 Pioglitazone 7.5 mg/day also caused lesser side effects like weight gain, increased BMI, increase in % body fat and had a lesser number of pedal edema cases as compared to pioglitazone 30 mg/day.

7.3 Hence it is prudent to start pioglitazone add on therapy at dose of 7.5 mg/ day in type 2 diabetes patients.

Some studies showed that low-dose of 7.5 mg of pioglitazone were associated with significant increase in plasma total adiponectin concentrations - which is associated with an improvement in insulin sensitivity.[27-30]

Conclusion

Till date, pioglitazone, the only antihyperglycemic agents available in India to directly decrease insulin resistance, have relatively potent A1C-lowering properties, a low risk of hypoglycemia, and durable glycemic effects. Pioglitazone in lower dose of 7.5 mg/day offers similar HbA1c reduction property as moderate dose of 30 mg/day pioglitazone with lesser incidence of side effects. Therefore, it is recommended to start pioglitazone 7.5 mg/day as add on therapy in type 2 diabetes patients.

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