



Point of View

Pioglitazone Safe, So Save

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Introduction

The scenario of treating diabetes is changing with steps of invention of different groups of drugs. Initially treatment was centred upon insulin replacement or stimulating insulin secretion. Nevertheless, the most important aetiology of Type 2 Diabetes mellitus (T_2DM) is insulin resistance. With invention of biguanides in 1950's, treatment started to focus on amelioration of insulin resistance. The treatment cascade has further been strengthened by invention of thiazolidinediones (Rosiglitazone, Pioglitazone), which act through Peroxisome Proliferators Activated Receptor (PPAR) γ as agonist. They act upon insulin resistance synergistically with metformin and exert different important non-glycaemic effects. They act upon majority of the components of insulin resistance like adiposity, dyslipidaemia, hyperglycaemia, hypertension, cardiovascular abnormalities, hyper coagulation, vasculopathy, accelerated atherosclerosis, and changes in liver and ovary.

Actions of Thiazolidinediones

Probably thiazolidinediones exert their primary action on the adipocyte. The effect is also on skeletal muscles, liver and other tissues to improve insulin action and secondary action due to changes in FFA, adiponectin and some other signals. In the pancreatic beta cell, they improve beta cell function, insulin sensitivity and prevent apoptosis of beta cells. In the endothelial wall they lower adhesion molecule and retards atherosclerotic progression.

Thiazolidinediones are potent anti-hyperglycaemic agents when used in proper dosage, the effect is more or less comparable to the effects of sulphonylurea, and metformin as seen in the treatment of type 2 DM. When combined with sulphonylurea, thiazolidinediones exert additional effect on blood sugar lowering capacity. Both the thiazolidinediones if combined with already existing metformin therapy improve glycaemic state, beta cell function and insulin sensitivity.

Thiazolidinediones are also effective even if added at late part of diagnosis after use of metformin and sulphonylurea with unsuccessful glycaemic control. In one study, 35 T_2DM patients received PIOG or ROSI after inadequate control with sulphonylurea and metformin. After 72 months, 51% remained well controlled by achieving HbA1C of 6.9%, rest 49% patient required insulin therapy. This study established the utility of thiazolidinediones even at late stage and effect is maintained upto 6 years.¹

Thiazolidinediones combination with Insulin therapy not only improves glycaemic state, but also ultimately lowers the daily insulin requirement by its protective effect on beta cells. Thiazolidinediones improves insulin sensitivity in the periphery and in the liver, muscle and other organs rich in insulin receptors. This improvement is seen not only in type 2 diabetes but also in pre-diabetes (IGT and/or IFG), polycystic ovarian syndrome and some cases of Type 1 diabetes. In one study of 205 newly diagnosed treatment naive T_2DM patients, PIO was compared

with metformin. After 24 weeks the results of improvement in HbA1C (~1.3%) and FPG (~54 mg/dl) were similar in both group but insulin sensitively improved much higher with PIO (17.4%) than metformin (8.9%) as assessed by HOMA-S model.²

Thiazolidinediones and Insulin Sensitivity

PPAR γ receptors are expressed in human pancreatic islet cells and multiple studies have established the role of thiazolidinediones in improving beta cell function. Probably major effect is mediated through suppression of FFA. Improvement in beta cell function may also be due to improvement in insulin receptor sensitivity, glucotoxicity and lipotoxicity, oxidative stress etc.³

Thiazolidinediones and Adipocytes

Thiazolidinediones stimulates proliferation of pre-adipocytes to neo-adipocytes which can store more fat or fatty acids and prevents their release into the circulation. They act also on the important enzymes of the lipogenesis system.⁴ Visceral fat are more resistant to insulin action than subcutaneous fat and increased visceral fat aggravate the problems of metabolic syndrome.

On the reverse, reduction of visceral fat and increase in subcutaneous fat, which effectively respond to insulin action and subsequent FFA entry and storage, is a factor for improving the metabolism. The same phenomenon is observed with thiazolidinedione treatment in CT Scan assessment of visceral and subcutaneous fat. In recent years, more improved technologies like MRI and DEXA scan has also confirmed the same observation and additionally shown that PIO and ROSI both mobilizes hepatic fat to peripheral subcutaneous tissue with improvement in so called Non Alcoholic Steato-Hepatitis (NASH). They also reduce hepatic lipid content.⁶

Thiazolidinediones and Lipid Metabolism

In Type 2 DM, common lipid abnormalities observed are higher triglyceride level, lower HDL and moderately elevated LDL. In Indian sub-continent first two lipid abnormalities are more common. Out of LDL concentration again majorities are type β small dense type and highly pro-atherogenic in nature.⁷

Both PIO and ROSI alter the lipid parameters but not in uniform manner. These drugs increase LDL Cholesterol level by 10 to 15%.^{8,9} Nevertheless, favourably enough there is diminution of the atherogenic fraction of LDL (small dense LDL type B) and increase in less atherogenic fraction (highly buoyant type A particle) together with decreased affinity for oxidation.⁹ Both the drugs also raise HDL from 10 to 15%.^{8,9} But notable favourable effects on triglyceride level are seen with PIO than ROSI.

In a double blind head to head comparison of 802 type 2 diabetes patients with dyslipidaemia without lipid lowering drugs, diet alone were randomized into PIO 45 mg or ROSI 8mg for 24 weeks. Glycaemic control was same in both groups evident by lowering of HbA1C (0.7%). But triglyceride was diminished by 51.9 mg/dl by PIO but increased by ROSI upto 13.1mg/dl

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($p < .001$). Increase in HDL was greater (5.2 vs. 2.4 mg/dl, $p < .001$) and rise in LDL was less (12.3 vs. 21.3/dl, $p < .001$) with PIO than ROSI. More over LDL particle size increased more with PIO ($p < .005$) than ROSI.¹⁰ This study calls for specific use of PIO in T₂DM cases with dyslipidaemia preferentially.

Effects on Heart

In a study, PIO in nondiabetic insulin resistant hypertensive persons, significantly improved LV diastolic dysfunction without left ventricular mass regression by ameliorating insulin resistance.¹¹

One of the most important causes for hypertension in diabetes, which is very frequent, is impaired insulin mediated vasodilatation. This is due to endothelial dysfunction, enhancement of renal sodium absorption and increased sympathetic nervous system activity.⁷ Thiazolidinediones improve blood pressure by improving the toxic vasodilator response due to improvement in insulin resistance and subsequent improvement in peripheral resistance. They also ameliorate the insulin induced excess renal sodium and sympathetic over activity.⁷ In a meta-analysis of 37 clinical trials thiazolidinediones reduced systolic B.P. by 4.70 mm Hg and diastolic BP by 3.79 mm Hg compared to base line. Compared to placebo the reduction was 3.47 mmHg and 1.84 mmHg respectively.¹²

Thiazolidinediones also inhibit accelerated vascular atherosclerosis by its action on endothelial, monocyte / macrophage and vascular smooth muscle cells. With these mechanisms, thiazolidinediones inhibit thrombogenicity, stabilises the atherosclerotic plaque if present. These changes have been reflected in studies showing improvement in both carotid intimo-medial thickening by Doppler study¹³ and in neo-intimal tissue proliferation after coronary stenting in intravascular ultra sound studies.¹⁴

Thiazolidinediones and Liver

A large group of patients of diabetes suffer from Non Alcoholic Fatty Liver Disease (NAFLD). Thiazolidinediones improve the condition both symptomatic and histological changes. Administration of PIO for 6 months has shown these results in a recent trial.¹⁵ Thiazolidinediones mobilizes intra hepato-cellular fat, inhibits inflammation and subsequent damage in NAFLD.

Thiazolidinediones and Ovary

Polycystic ovarian syndrome consists of hyper-androgenism, chronic anovulation, obesity and other features of insulin resistance. Thiazolidinediones exert insulin sensitizing and ovulation induction effect in women with this syndrome.¹⁷

Thiazolidinediones and Malignancy

Thiazolidinediones have anti-tumour activity because of expression of PPAR- γ receptor in neoplastic cell line of colon, breast, and pancreas, prostate and leukaemia. Other than PPAR- γ activity, this anticancer effect is also due to PPAR- γ independent activity and anti-angiogenic activity.^{19,20} But this in vitro data was not reflected in human trials with colorectal and prostatic carcinoma.¹⁹ Rather in murine models, this drug showed some tumour inducing activity and hence they should be avoided in patients with adenomatous polyposis coli.¹⁹

PPAR γ agonists have several anticancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation, and PPAR γ is currently considered a potential target for both

chemoprevention and cancer therapy based on other preclinical studies.²⁰ Studies in rodents have shown that PPAR agonists can potentiate tumorigenesis, and are multispecies, multisex carcinogens. Therefore, TZDs may increase, decrease, or have a neutral effect on the risk of cancer or cancer progression in humans.²¹

Definitive human data regarding the cancer risk associated with TZDs are not available. Meta-analysis of clinical trials of rosiglitazone demonstrated no statistically significant increase or decrease in the risk of cancer though the numbers of cancer cases at these specific sites were small.²² This epidemiologic studies examined only short-term exposure, due to recent introduction of these medications and the shorter duration of many trials. Few clinical trials conducted of TZDs for cancer treatment, show negative results

Ferrara A et al²² found no clear evidence of an association between use of pioglitazone and risk of the incident cancers examined and as because the maximum duration of follow-up was fewer than 6 years after the initiation of pioglitazone, longer-term studies are needed.

Long Term Safety Profile

Thiazolidinediones are considered as a very useful antidiabetic, acting as potent insulin sensitizer. They can be combined with other antibiotics but with caution with insulin in cases with heart failure and oedema. They are slower in action but of longer duration. Their glycaemic effect is comparable with sulphonylurea and metformin. Other than glycaemic effect, they have multiple favourable effects. Unfortunately, the drug is under utilized in the treatment strategy of diabetes.

Recent Debate

Recently a bubbling has been created for banning the drug with the allegation of incidence of cancer. It is really bad news for patients and doctors and the Drug Company, but good news for Law Graduates!! Not a single trial based on this issue is a prospective well balanced one where pioglitazone was started after screening for cancer. Diabetes itself is a precancerous condition, carcinogenesis may be due to other drugs used concomitantly with pioglitazone. As drugs can kill a person, there are persons who have killed multiple drugs also. As discussed above, presently pioglitazone is such a drug that provides us all the requirement of an antidiabetic agent more so in affordable price. If we banish it, we will have to switch over to injections (insulin or incretin mimetics) or ultra costly gliptins. It has been suggested that metformin, pioglitazone and GLP1 agonists may represent the optimum combination of agents for the modern management of type 2 diabetes based on the pathophysiology of the disease. If pioglitazone use is suspended many patients will experience worsening of glycaemic control and risk from acute hyperglycaemic syndromes as well as potentially increased microvascular and macrovascular damage. Pioglitazone will shortly emerge from patent and with the exception of sulphonylureas there are no other popular alternative low cost pharmaceutical options.

A substantial number of people with diabetes are on triple oral hypoglycaemic therapy including pioglitazone so in the event of total withdrawal, many will need to change to expensive options including injectables (a major stress on specialist resources nationally) or gliptins. A number of occupational drivers may lose their licence as a result of a total withdrawal of pioglitazone –these include occupational drivers on pioglitazone alongside GLP1-based treatment most of whom will migrate to

insulin or be inadequately controlled.

Glitpins have an increasing market share and are a pressure on pharmaceutical budgets. Although heavily marketed across the UK, India and other countries there are no long term safety data available and there are concerns that the ubiquity of the enzyme system which they inhibit might predispose to long term safety issues. Many people with diabetes will therefore be moving from one drug with a possible safety problem to another with an unknown long term safety record. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy. Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency.

European Medicines Agency (EMA) Update²⁴

As published by Shelly Wood on 21st July, The European Medicines Agency (EMA) has reached a decision in its review of pioglitazone, opting to recommend new contraindications and warnings be added to the drug label, noting that there is a small increased risk of bladder cancer with the diabetes drug. The EMA's alert concludes that the "benefit/risk balance remains positive in a limited population of type 2 diabetics" and 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." Risk factors for bladder cancer should be "investigated," particularly in elderly patients, before physicians move forward with the choice of pioglitazone, the EMA alert states. Patients in whom pioglitazone should not be considered include those with current or a history of bladder cancer or those with uninvestigated macroscopic haematuria.

The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that, although there is a small risk of bladder cancer with pioglitazone, its benefits continue to outweigh its risks in a limited population of type 2 diabetes patients. The issue of the possible risk of bladder cancer was raised at the time of marketing authorisation of the first pioglitazone-containing medicines in 2000. At that time, some preclinical studies identified cases of bladder cancer in male rats, but the evidence did not point to a risk in humans.

At the time of authorisation, the company committed to perform a population-based study (KPNC)(25) on the long-term safety of pioglitazone. The study is still ongoing and the Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed preliminary results showing a small risk of bladder cancer in the patients treated with pioglitazone.

In a clinical trial (PROactive)²⁶ more bladder cancer cases were reported for pioglitazone than placebo, and there has been a higher than expected number of reports of bladder cancer in patients taking pioglitazone in the EU and the United States. The CHMP has been studying the data as they have become available and, although they are inconclusive on their own, the accumulated evidence pointed to a signal of bladder cancer that warranted a full review.

The CHMP carried out this review to establish whether, in light of the evidence regarding bladder cancer, the marketing authorisations for pioglitazone-containing medicines should be maintained, varied, suspended or withdrawn across the EU.

As the CHMP was carrying out its review, new data emerged from a population-based study in France which also pointed to a risk of bladder cancer with pioglitazone, prompting the French medicines agency to suspend the use of the medicines in France. Germany and Luxembourg took the precautionary measure of recommending that doctors not start new patients on pioglitazone while the review was ongoing.

What are the Conclusions of the CHMP?

The CHMP concluded that the evidence from different sources shows that there is a small risk of bladder cancer with pioglitazone. Recent data from population-based studies (the KPNC study, the French study, and a GPRD 2 case control study) showed a risk of bladder cancer, particularly in patients treated for the longest periods and at the highest doses.

In an analysis of several clinical trials together (a meta-analysis), 19 out of 12,506 patients taking pioglitazone had bladder cancer (0.15%) compared with 7 out of 10,212 patients not taking pioglitazone (0.07%).

The CHMP noted that there are some patients who cannot be adequately treated by other treatments and who will benefit from pioglitazone. Considering the risks associated with pioglitazone and its benefits to some patients, the CHMP concluded that the benefits outweigh the risks in those patients responding well to pioglitazone. Prescribers are advised to carefully select patients and monitor how they respond to treatment.

The CHMP also made recommendations in the prescribing information to reduce the risk of bladder cancer. These recommendations cover the monitoring of the effects of treatment, restrictions in its use and factors that prescribers and patients should take into account when using pioglitazone-containing medicines.

What are the Recommendations for Prescribers?

Prescribers are reminded that the benefits of pioglitazone continue to outweigh its risk in patients responding adequately to treatment, but that certain measures will need to be taken to reduce the risk of bladder cancer.

Some patients will need to be taken off pioglitazone, such as those who have or have had bladder cancer or those with blood in the urine that has not yet been investigated.

Prescribers should review the treatment of new patients and patients currently on pioglitazone after three to six months, and discontinue treatment for those who are not deriving sufficient benefit. At subsequent reviews prescribers should confirm that benefits to patients are maintained.

Prescribers should consider patients' risk factors for bladder cancer (such as age, smoking and exposure to certain chemicals or treatments) before starting them on pioglitazone.

Prescribers should start elderly patients on the lowest possible dose, as they are at a higher risk of bladder cancer, as well as heart failure, with pioglitazone.

What are the Recommendations for Patients?

Patients should immediately report any blood in their urine or other symptoms of a bladder condition (such as pain while urinating or urinary urgency) to their doctor.

Patients currently on pioglitazone will have their treatments evaluated by their doctor at their next scheduled appointment. Patients with any questions should speak to their doctor.

A European Commission decision on this opinion will be issued in due course.

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, the CHMP has asked the marketing authorisation holder to conduct a pan-European epidemiological study focussing 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.

Opinion of ABCD

ABCD is the national Association of British Clinical Diabetologists in the UK. Dr C. Walton, Honorary Chairman of ABCD is of the opinion that “pioglitazone is the only glycaemic medication other than metformin with randomised controlled trial evidence that it reduces death, myocardial infarction and stroke. If it is suspended prematurely we may be losing an agent with such benefit for the sake of as yet uncertain, unproven risk. Pioglitazone is particularly beneficial in reducing the chances of a patient who has had a stroke from having further stroke”.

A meta-analysis of pioglitazone trials showed that among a diverse population of patients with type 2 diabetes, pioglitazone treatment was associated with a significantly lower risk of death, myocardial infarction or stroke.²⁷ A retrospective cohort study using the UK general practice research database (91521 patients with diabetes) suggested that pioglitazone was associated the lowest all cause mortality amongst the oral hypoglycaemic agents.²⁸

Randomised controlled trials of markers of carotid and coronary atherosclerosis (Carotid intima-media thickness and intravascular ultrasound) have shown benefit for pioglitazone compared to sulphonylureas.²⁹ The primary composite endpoint in the PROactive study did not achieve statistical significance.²⁶ Nevertheless, the first six factors in the primary composite endpoint: death, non fatal myocardial infarction, silent myocardial infarction, stroke, major leg amputation and acute coronary syndrome do show significant benefit for pioglitazone. Statistical significance is lost only when coronary and leg revascularisation is added. It has been suggested that this outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome and leg amputation to be available for coronary or leg revascularisation. This interpretation suggests a real benefit of pioglitazone in the treatment of Type 2 diabetes.

Pioglitazone is widely prescribed in the UK and there are many patients who are stable with good glycaemic control on this agent. We believe that pioglitazone is making a major contribution to the improvement in glycaemic control amongst our patients – and it is accepted that improved glycaemic control is associated with improved microvascular outcomes.³⁰

The most powerful evidence with regard to side effects of pioglitazone come from the PROactive study as it is the only randomised controlled trial. We note that there were more bladder cancers in the pioglitazone group, although this did not achieve significance. There were significantly fewer breast cancers in the pioglitazone group.²⁶

We note that a publication in the current issue of Diabetes

Care concerns spontaneous reports of bladder cancer the FDA Adverse Event Reporting System.³¹ It is of course possible that as it is well known that the link between bladder cancer and pioglitazone is being actively pursued, it is quite likely that bladder cancers are more likely to be reported in pioglitazone treated patients than in non pioglitazone treated patients..

We note that interim analysis of the Kaiser Permanente longitudinal cohort study found that overall ever use of pioglitazone was not associated with risk of bladder cancer but use for more than 2 years was weakly associated with increased risk.²⁵ This is obviously of concern for long term use. The authors of that paper do acknowledge that there were proportionately more in situ cancers among the pioglitazone users and that this might be observed if pioglitazone-treated patients underwent greater surveillance for bladder cancer.

ABCD wishes to strongly encourage Medicines and Healthcare Products Regulatory Agency London (MHRA) to resist EMA following the French and German lead with regard to pioglitazone, pending ongoing long term investigations.

While ABCD deems patient safety to be paramount, we are concerned that far more harm than good will be done if pioglitazone is suspended and that on current evidence the risk/benefit balance is strongly in favour of continuing the current licence for the use of pioglitazone to reduce the risks of diabetes-driven morbidity and mortality. In the making of decisions ABCD believes that all factors should be taken into account including macrovascular benefits of pioglitazone, the contribution of pioglitazone to good glycaemic control and associated microvascular benefits and the threat of glycaemic deterioration if pioglitazone is withdrawn. A position aligned with that of the FDA, which recommends withdrawal of pioglitazone only in those with active bladder cancer, and a risk benefit analysis in those with previous cancer, would seem a sensible interim position.

Opinion of FDA

The FDA from USA has issued the following recommendations for health care professionals³²

- do not use pioglitazone in patients with active bladder cancer;
- use pioglitazone with caution in patients with a prior history of bladder cancer;
- weigh the benefits of blood sugar control with pioglitazone against the unknown risks of cancer recurrence;
- counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain during urination, or back or abdominal pain, as these may be due to bladder cancer;
- encourage patients to read the medication guide;
- report adverse events to the FDA

Opinion of Australian Government Department of Health and Ageing

As a safety advisory on 18 July 2011 The Therapeutic Goods Administration (TGA) a division of the Australian Government Department of Health and Ageing, is advising health professionals and consumers that use of the diabetes medicine, pioglitazone, for more than a year may be associated with an increased risk of bladder cancer.

Incidence of bladder cancer varies from group to group, depending on risk factors such as age, gender, cigarette smoking and occupational exposure to certain chemicals. The Australian

Institute of Health and Welfare estimated there would be around 2500 new cases of bladder cancer in Australia for 2010, about three-quarters of these in males.³³

TGA has passed the information for Health Professionals more or less similar as FDA.

Conclusion

Some confusion has arisen amongst us because of triggering the panic button of cancer development out of pioglitazone. Recently same type of attack was targeted on insulin glargine and ARB's, which could not be ultimately substantiated. My personal interaction with physicians in India have convinced me to accept that, pioglitazone should stay till we get a better drug which provides all the actions of pioglitazone in affordable price. Before that we should not sacrifice our patients for injections and costly medicine because of over zealous caution.

We should not be the first person to accept a new thing (read without proper assessment), and also not be the last person to discard it (read when really proved beyond doubt). When we venture for the rose, we should concentrate on its smell and beauty not on the thorns only, otherwise we will be looser.

References

- Bell DS, Ovalle F. Long-term glycaemic efficacy and weight changes associated with thiazolidinediones when added at an advanced stage of type 2 diabetes. *Diabetes Obese Metab* 2006;8:110-5.
- Paavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patient with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88:1637-45.
- Prigeon RL, Kahn SE, Porte D. Effect of troglitazone on B cell function, insulin sensitivity and glycemic control in subjects with type 2 diabetes mellitus. *J Clin Endo Metab* 1998;83:819-923.
- Spiegelman BM. PPAR: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 1998;47:507-14.
- Mori Y, Murakawa Y, Okada K, et al. Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 1999;22:908-12.
- Carey DG, Cowin GJ, Galloway GJ, et al. The effects of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients. *Obse Res* 2002;10:1008-15.
- Sunder Mudaliar and Robert R. Henry, Thiazolidinediones in Type 2 Diabetes Principles and Practice, Second Edition Edited By Barry J. Goldstein, Dirk Muller-Wieland, 2008 Informa
- Actos (Prescribing information). Lincolnshire, II: Takeda; Indianapolis, IN: Elli Lily Company, 2002.
- Freed MI, Ratner R, Marcovina SM, et al. Rosiglitazone Study 108 investigators. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol* 2002;90:947-52.
- Goldberg RB, Kendall DM, Deeg MA et al. GLAI Study Investigators. A comparison of lipid and glycemic effects of Pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;28:1547-54. healthcare New York London
- Horio T, Suzuki M, Suzuki K, et al. Pioglitazone improves left ventricular diastolic function in patients with essential hypertension. *Am J Hypertens* 2005;18:949-57.
- Qayyum R, Adomatyte J. A meta-analysis of the effect of thiazolidinediones on blood pressure. *J Clin Hypertens (Greenwich)* 2006;8:19-28.
- Koshiyama H, Shimono D, Kuwamura N, et al. Inhibitory effect of Pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:3452-6.
- Choi D, Kim SK, Choi SH, et al. Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes. *Diabetes Care* 2004;27:2654-60.
- Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of Pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl Med* 2006;355:2297-307.
- Purnell JQ, Dev RK, Steffes MW, et al. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes control and Complications Trial. *Diabetes* 2003;52:2623-9.
- Dunaif A, Scott d, Finegood D, et al. The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1996;81:3299-306.
- Panigrahy D, Singer S, Shen LQ, et al. PPAR- γ independent induction of growth arrest and by inhibiting angiogenesis. *J Clin Invest* 2002;110:923-32.
- Derosa G, Ceiro AF, Gaddi A, et al. A comparison of the effects of pioglitazone and rosiglitazone combined with glimepiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome. *Diabetes Res Clin Pract* 2005;69:5-13.
- Panigrahy D, Huang S, Kieran MW, Kaipainen A. PPAR γ as a therapeutic target for tumor angiogenesis and metastasis. *Cancer Biol Ther* 2005;4:687-693
- Clay CE, Namen AM, Atsumi G, et al. Magnitude of peroxisome proliferator-activated receptor- γ activation is associated with important and seemingly opposite biological responses in breast cancer cells. *J Investig Med* 2001;49:413-420.
- Monami M, Lamanna C, Marchionni N, Mannucci E. Rosiglitazone and risk of cancer: a meta-analysis of randomized clinical trials. *Diabetes Care* 2008;31:1455-1460
- Lewis JD, Ferrara A, Charles P, Quessenberry J, Peng T, Strom BL et al. Risk of bladder cancer among diabetic patients treated with pioglitazone. *Diab Care* 2011;34:916-22.
- www.ema.europa.eu d Accessed on 21/7/2011
- Friedman G, Habel L, Boles M, McFarland B, Kaiser Permanente Medical Care Program: Division of Research, Northern California, and Center for Health Research, Northwest Division. In Pharmacoeconomics. 3rd ed. Strom BL, Ed. West Sussex, U.K., John Wiley & Sons, 2000;263-283
- Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-1289.
- Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180-1188.
- Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009 Dec 3;339:b4731. doi: 10.1136/bmj.b4731.
- Mazzone T, Meyer PM, Feinsein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006;296:2572-2581.
- Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes UKPDS Group. *Lancet* 1998;352:837-853
- 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;34:1369-71. Epub 2011 Apr 22.
- WWW.fda.gov?safty/Medwatch/saftyinformation/human medicinal products/ucm226257.htm/accessed on 21st July 2011
- Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2010. Cancer in Australia: an overview, 2010. Cancer series no. 60. Cat. no. CAN 56. Canberra: AIHW.