

Current developments in thiazolidinediones

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Abstract: The invention of thiazolidinediones, also referred to as glitazones, has been one of the greatest developments in the treatment of Type II diabetes over the last two decades. Although the efficacy of the glitazones is substantial, their use has been limited by adverse effects including edema, weight gain and cardiac issues. While still being used for a specific subset of diabetic patients, much effort is being expended to find other therapeutic uses for the glitazones, especially to take advantage of their anti-inflammatory benefits. Progress is also being made in the development of more selective PPAR- γ agonists that would offer the same efficacy as the thiazolidinediones, but with reduced adverse effects.

Introduction:

The thiazolidinediones belong to the class of drugs that are PPAR- γ (peroxisome proliferator-activated receptor- γ) agonists. By stimulating PPAR- γ , the thiazolidinediones increase the insulin sensitivity of cells throughout the body, especially adipose tissue, and hence they have been used with great success in the treatment of Type II diabetes.

There are currently two thiazolidinediones on the market; rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda Pharmaceuticals). Based on the ending of their generic names, these drugs are also referred to as glitazones. Rosiglitazone was once the largest selling diabetes therapy in the world with sales of \$3.3 billion in 2006, while pioglitazone had sales of \$2.8 billion.

The glitazones have been shown in numerous clinical studies to provide a significant reduction in blood glucose levels, but rosiglitazone was linked to a 43 percent increase in the risk of heart attacks, resulting in as many 50,000 excess heart attacks in the millions of patients exposed to it.¹

In July 2010, an FDA advisory panel voted to keep rosiglitazone on the market, albeit with a tougher warning on the label. The negative assessment was due in part to the fact that the risk of myocardial infarction was thought to be 30% to 80% higher among patients taking rosiglitazone than with placebo. In the beginning of this year, GSK had to set aside \$3.5 billion for product liability cases, in addition to a \$2.36 billion charge of last summer. Pioglitazone does not seem to share the same risk and may even protect diabetic patients against myocardial infarction, but sales of pioglitazone have not increased substantially as rosiglitazone's have declined.

In this article, I briefly review the mechanism of action of the thiazolidinediones, their benefits and adverse effects,

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and what the future may hold for repurposing of glitazones for other indications (such as asthma and other inflammatory conditions) and the development of selective PPAR- γ modulators that offer the promise of equivalent efficacy with reduced adverse effects.

Mechanism of Action:

Thiazolidinediones decrease insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator-activated receptor- γ (PPAR- γ). Activation of PPAR- γ leads to a myriad of effects on gene regulation, including increases in proteins involved in glucose uptake.

By increasing the sensitivity of adipocytes and other somatic cells to insulin, the glitazones, like metformin, promote the absorption of glucose into cells and by this action lower blood sugar levels. Unlike, the insulin secretagogues, such as sulfonylureas and gliptins, PPAR- γ agonists do not increase insulin levels, and hence they are less likely to decrease glucose too rapidly, leading to a hypoglycemic state.

Benefits:

The primary benefit of the glitazones is controlling hyperglycemia in Type II diabetes. Treatment for diabetes is aimed at lowering fasting blood glucose levels to normal levels (<100 mg/dL) and reducing the concentration of HbA1c, the glycosylated form of hemoglobin. During the finite lifetime of red blood cells, hemoglobin molecules become glycosylated, forming HbA1c. Higher levels of HbA1c indicate long-term exposure to elevated levels of blood glucose. This is in contrast to an instant measure of glucose, which indicates a "snapshot" of blood sugar levels. Both rosiglitazone and pioglitazone act similarly in improving glucose levels, typically decreasing HbA1c levels by about 0.5%.

There is some indication that insulin sensitizers, such as the glitazones, may preserve β -cell function or mass more than insulin secretagogues, such as sulfonylureas. In one study, pioglitazone cut in half the progression of patients to

needing insulin.² The DREAM On (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up) study found that rosiglitazone reduces the long-term incidence of diabetes by delaying the underlying disease process, although not reversing it.³

The glitazones have several other positive 'side effects.' Rosiglitazone increases HDL-cholesterol levels and reduces high-sensitivity C-reactive protein.⁴ Thiazolidinediones have been found to decrease the urinary excretion of albumin and other proteins and interfere with the development and progression of diabetic nephropathy.⁵ In terms of economics, glitazones are cheaper than some of the newer diabetes treatments, such as exenatide, glargine, detemir and similar in cost to insulin regimens.

Adverse Effects:

Both rosiglitazone and pioglitazone are associated with edema, heart failure and, in women, bone fractures.

Rosiglitazone slightly increases the risk of cardiovascular events, such as heart attacks and mortality, while pioglitazone appears to reduce the risk for all-cause mortality, non-fatal myocardial infarction and stroke, even though it increases the occurrence of heart failure.⁶ The differences between rosiglitazone and pioglitazone may be due to differences in effects on blood lipids, with pioglitazone producing a greater decrease in triglycerides, less of an increase in total cholesterol and an increase in HDL cholesterol. Rosiglitazone may also impair endothelial function by interfering with nitric oxide bioavailability.⁷

One meta-analysis showed that rosiglitazone increased the risk of cardiovascular disease by 40% compared to metformin, sulfonylurea or placebo. Other analyses have shown non-significant differences, or significant effects for myocardial infarction and heart failure, but not for overall cardiovascular mortality. In 2007, the FDA concluded that rosiglitazone carried a higher risk of myocardial ischemic events than placebo, metformin or sulfonylureas, but did not recommend taking it off the market at that time. For rosiglitazone, the increase in risk is low, but still disappointing considering that the use of hypoglycemic drugs is aimed at reducing the sequelae of diabetes, including cardiovascular morbidity. While rosiglitazone increases the occurrence of non-fatal myocardial infarction, it is not yet associated with increased cardiovascular death.

PPAR- γ activation is thought to be related to bone fractures by suppressing osteoblastogenesis (bone formation) and stimulating osteoclastogenesis (bone resorption).⁸ Swelling from glitazones may cause macular edema, which does not appear to resolve even after stopping medication.⁹ While rosiglitazone displays significant improvements in glycemic control and insulin sensitivity, it does not have positive

effects on the inflammatory markers of carotid arterial disease.¹⁰

Pioglitazone can produce slight weight gain, in some studies an average of 3 kg. Due to their mechanism of action, the glitazones should not be likely to cause hypoglycemic events, yet pioglitazone produced marginally more low glucose episodes. The overall benefit of pioglitazone is slight, as an economic analysis reported that use of pioglitazone leads to an increase in life expectancy of just 0.0109 years (i.e., 4 days).

In microarray studies, the benefits of rosiglitazone are clearly seen by its normalization of gluconeogenesis-related genes. However rosiglitazone also up-regulated many genes implicated in lipid synthesis, such as ATP citrate lyase and fatty acid synthase. Because of their adipogenic effects, PPAR- γ agonists, including the thiazolidinediones, have been bestowed with the unfortunate moniker of obesogens.¹¹ This term refers to exogenous compounds that disrupt normal metabolism of lipids leading to obesity. Beyond their insulin sensitizing effect, PPAR- γ agonists are known to promote fat cell differentiation and fat storage.

The glitazones are marginally more expensive than gliptins, such as sitagliptin and vildagliptin, but do not offer any clinical advantage. Gliptins also appear to have fewer long-term side effects and less weight gain.

Current Status

Since metformin and glitazones have different mechanisms of action, acting on glucose production and glucose distribution respectively, it is rational to combine the two with the expectation of low occurrence of hypoglycemia.

The NICE 2008 guidelines recommend using a glitazone (either rosiglitazone or pioglitazone) if after use of sulfonylureas, HbA1c levels remain above 7.5%. The earlier guidelines (2003) recommended glitazones in combination with metformin or sulfonylureas for those who could not take the combination of metformin with a sulfonylurea. There is some off-label use of all three if metformin and a sulfonylurea do not produce a desired reduction in HbA1c. The NICE guidelines also suggest the use of thiazolidinediones if there is a problem with hypoglycemia with the use of sulfonylureas. EMEA 2008 guidelines allow glitazones used alone, in combination with metformin or sulfonylurea, and in triple therapy.

In general, prescribing data indicate that there has been a reduction in the use of rosiglitazone, but patients are being shifted to gliptins rather than pioglitazone. The dipeptidyl peptidase-4 (DPP-4) inhibitors, whose generic names end with gliptin, stop the metabolism of incretins and so provide similar benefits. Gliptins may be substituted for

thiazolidinediones, since they appear to cause fewer long-term effects.

Competition for the glitazones also includes direct use of incretin-like molecules, such as the GLP-1 analogue exenatide. Incretins function not by affecting insulin directly, but by suppressing glucagon secretion which slows gastric emptying, decreases appetite and perhaps increases β -cell mass. Like the glitazones, incretins do not induce hypoglycemia, however unlike the glitazones, they are less likely to cause weight gain and may even yield a slight weight loss.

Pioglitazone is used only as a first-line treatment when metformin is contraindicated. Following metformin treatment, sulfonylureas and then glitazones are commonly used, with the latter being the most expensive treatment of the three. Some practitioners are advocating earlier use of insulin, especially combinations of insulin that are delivered at different rates to more closely mimic the body's natural secretion pattern.

Repurposing:

While sales of thiazolidinediones for treatment of diabetes are likely to decline, efforts are being made to find other applications for them, or "repurposing". Clinical studies are underway in cancer, stroke, and inflammatory diseases, such as asthma.

Cancer

The anticancer properties of the thiazolidinediones have been examined in pituitary and adrenocortical cancer, where rosiglitazone inhibits cell proliferation through arrest at the G0/G1 cell-cycle and induction of apoptosis. Another PPAR- γ agonist, DK2, has been shown to inhibit pterygium fibroblasts, also arresting cell growth at the G0/G1 phase and inducing apoptosis.¹²

Both statins and thiazolidinediones exhibit potent pro-apoptotic activity. The combination of statins with rosiglitazone or pioglitazone demonstrated significant cytotoxic effects on malignant glioma cells.¹³ Thiazolidinediones and other PPAR- γ agonists display these anti-tumor apoptosis effects in some human prostate cancer cell lines. Combinations of thiazolidinediones with fatty acid synthase inhibitors showed synergistic anti-prostate tumor properties.¹⁴ Surprisingly, both rosiglitazone and pioglitazone have provided generally unsatisfactory results to date in the treatment of Cushing's disease.¹⁵

Liver Disease

Reduced levels of adiponectin are thought to be one of the causes of non-alcoholic steatohepatitis (NASH). Through its PPAR- γ activity, rosiglitazone increased circulating levels of

adiponectin and improved the histological liver lesions characteristic of NASH.¹⁶ Both rosiglitazone and pioglitazone are highly effective at reducing liver fat content, and possibly also hepatocellular damage of NASH.¹⁷

Stroke

Several studies have shown that thiazolidinediones may prevent or lessen the central nervous system injury that follows an ischemic event. Both glitazones were effective in reducing the volume of the infarct and protecting nerve function. Pretreatment with a thiazolidinedione does not appear to be required for neuroprotection making them a potential therapy for ischemic stroke.¹⁸

Pioglitazone has been shown to inhibit ischemia-induced brain injury. Its neuroprotective effects are thought to be associated with PPAR- γ mediated suppression of the NF- κ B inflammatory signaling pathway.¹⁹ By increasing superoxide dismutase/catalase and decreasing NADP oxidase levels, PPAR- γ agonists attenuated ischemia-induced reactive oxygen species and reduced post-ischemic degradation of apoptotic factors.²⁰

Pioglitazone and rosiglitazone induced the proliferation of neurosphere-forming cells, showing that PPAR- γ agonists can directly regulate proliferation, differentiation and migration of neural stem cells.²¹ After ischemic injury and reperfusion, PPAR- γ levels increase in microglia reducing further damage. Rosiglitazone delays neural injury by interfering with glial activation and increases the level of anti-inflammatory cytokines, such as IL-4 and IL-13.²²

Inflammation

PPAR- γ agonists can inhibit the inflammatory cytokines IL-1b, IL-6, IL-8 and TNF- α , while suppressing the expression of cyclooxygenase-2.²³ There is also evidence that PPAR- γ agonists can reduce migration of antigen-bearing dendritic cells and reduce the release of G-CSF and GM-CSF. Because of their regulation of epithelial cell inflammation, PPAR- γ agonists are being examined for treatment of acute lung injury, chronic obstruction pulmonary disease and asthma. Some of the beneficial aspects of thiazolidinediones do not seem to be effected by their PPAR- γ agonism. Thiazolidinediones inhibit a number of inflammatory mediators involved in the asthmatic response including RANTES.²⁴

The β -2 adrenoceptor agonist, salbutamol, is used to relax airway smooth muscle in asthma, but its continued use can lead to tolerance. It has been found that PPAR- γ agonists including rosiglitazone interact with salbutamol. This interaction can reverse the tolerance to β -2 agonists, suggesting a use in combination for preserving salbutamol relaxant activity in chronic airway disease.²⁵

Rosiglitazone and pioglitazone both significantly decrease serum levels of C-reactive protein, a biomarker and predictor of coronary artery disease. The thiazolidinediones exhibited this property in both diabetic and non-diabetic patients.²⁶ Amongst its anti-inflammatory activities, rosiglitazone has been shown to inhibit TGF- β signaling. This action has led to use of rosiglitazone for effective alleviation of the symptoms of psoriasis, in which deregulation of TGF- β signaling occurs.²⁷ Rosiglitazone has been reported to be effective in both autoimmune diseases such as multiple sclerosis and inflammatory diseases including ulcerative colitis. Based on their anti-inflammatory activity, thiazolidinediones and other PPAR- γ agonists are being considered for such conditions as inflammatory bowel disease and rheumatoid arthritis.²⁸

Selective PPAR- γ Modulators:

Within the last 10 years, new PPAR- γ agonists have been developed that display insulin-sensitizing activity with lower stimulation of adipogenesis.

Selective modulation of PPAR- γ may provide desirable therapeutic effects without the adverse effects of full activation. Ligand binding to PPAR- γ affects the co-receptor RXR (retinoid X receptor) and an array of co-regulators that control gene transcription. The degree of binding depends upon the conformational changes induced by the ligand (i.e., drug) that binds to the receptor. By careful design of the drug, specific co-regulators can be invoked, thus providing an opportunity for modulating the physiological response.²⁹ Ideally PPAR- γ should be modulated so that insulin-sensitizing activity is maintained, while fluid retention, bone fracture and cardiac effects are minimized. Selective PPAR- γ modulators (SPPAR γ M) could be safer alternatives to PPAR- γ full agonists, both for diabetes and other conditions. The next generation of SPPAR γ M may be effective insulin sensitizers with superior safety to current thiazolidinediones.³⁰

PPAR- γ ligands include a large set of endogenous compounds, such as prostaglandin PGJ₂, linolenic, eicosapentaenoic, docohexaenoic, and arachidonic acids, and synthetic ligands, including the thiazolidinediones and nonsteroidal anti-inflammatory drugs. SPPAR γ M bind in distinct manners to the ligand-binding pocket of PPAR- γ . The specific binding leads to the possibility of alternative receptor conformations and cofactor recruitment, producing differential gene expression and biological responses.³¹ What appears to make a good SPPAR γ M is preferential recruitment of particular co-factors. One especially good co-factor to recruit is PGC1- α , which is associated with increased energy expenditure, but not energy storage.

One of the SPPAR γ M that is under clinical investigation is metaglidasen, which acts as a partial PPAR- γ agonist/antagonist. With its modified selectivity, metaglidasen shows only moderate adipogenesis and attenuated fatty acid uptake and synthesis, with the potential for reduced weight gain. INT131 (InteKrin Therapeutics) is a sulfonamide specifically designed as a non-thiazolidinedione PPAR- γ agonist that displays similar efficacy to rosiglitazone but without fluid retention or cardiac hypertrophy.

Other thiazolidinediones, such as balaglitazone and netoglitazone act as partial PPAR- γ agonists, hence only partially induce adipogenesis and weight gain. Angiotensin receptor blockers were recently characterized as a SPPAR γ M. Telmisartan is a partial agonist of PPAR- γ that appears to improve insulin sensitivity without appreciable weight gain. A recently developed thiazolidinedione purports to activate PPAR- γ as well as any of the glitazones, but has anti-obesity effects while lowering triglyceride and total cholesterol levels.³² This compound may convey additional benefits by its inhibition of the protein-tyrosine phosphatase 1b (PTP1b) enzyme, a negative regulator of the insulin-signaling pathway.

SPPAR γ M promise new benefits, but can also produce unexpected adverse effects. Many of the glitazars, a new class of PPAR- γ agonists, have been abandoned because of serious side effects and carcinogenesis-related issues. In the last decade more than 50 PPAR- γ agonists have failed during clinical development.¹ Nevertheless, development continues at a rapid pace.

Conclusions:

Use of rosiglitazone for type II diabetes will likely continue to decline. This loss in market share of rosiglitazone does not seem to be benefiting pioglitazone greatly, although use will probably either remain steady or slowly increase as the diabetes markets grows. The anti-inflammatory benefits of the glitazones may lead to repurposing of these drugs for other conditions, including cancer, liver disease, stroke, chronic airway disease and many others. Development of new SPPAR γ M promises selective action that can provide benefits in hyperglycemic control without adipogenic side effects. While it has been a tough few years for the thiazolidinediones, there are still many exciting opportunities ahead for this unique class of drugs.

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