

## METABOLIC EFFECTS OF THIAZOLIDINEDIONES

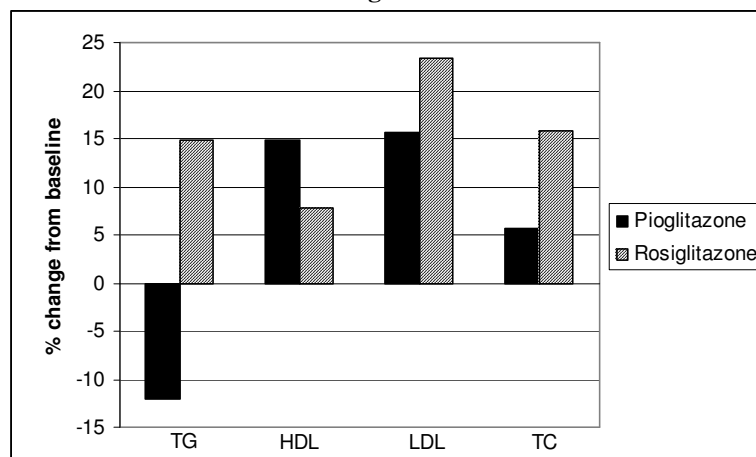
### Background

Although the thiazolidinediones (TZDs), pioglitazone (Actos<sup>®</sup>) and rosiglitazone (Avandia<sup>®</sup>), have similar efficacy in terms of glycemic control, recent studies have highlighted concerns regarding their metabolic effects, especially lipid abnormalities and fluid retention.<sup>1,2</sup>

### Lipid Abnormalities

- Research suggests that pioglitazone and rosiglitazone differ in their effects on lipids
  - A July 2005 study in *Diabetes Care* found pioglitazone to be superior to rosiglitazone in several lipid parameters, the largest difference being reflected in triglyceride levels (see Figure I)<sup>2</sup>

Figure I



TG: triglycerides, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TC: total cholesterol

- Both agents were also shown to make LDL particles larger and less dense, thus making them less atherogenic. However, the increase in the number of particles with pioglitazone was less than the increase with rosiglitazone.<sup>2</sup>
- The mechanism behind this difference is hypothesized to be due to receptor subtype affinity:
  - Both TZDs stimulate the peroxisome-proliferator-activated receptor (PPAR) gamma, resulting in improved insulin sensitivity and increased glucose uptake
    - PPAR-alpha is another member of this family of receptors, the activation of which results in increases in HDL cholesterol and decreases in triglycerides
      - The fibrates (gemfibrozil (Lopid<sup>®</sup>) and fenofibrate (Tricor<sup>®</sup>) are examples of agents that work via this mechanism
    - Pioglitazone, but not rosiglitazone, appears to activate PPAR-gamma and PPAR-alpha, thus leading to its beneficial effects on lipid parameters<sup>1,3</sup>

### Fluid Retention

- Both pioglitazone and rosiglitazone are equally associated with fluid retention with reported exacerbations of CHF, especially when they are used in combination with insulin
  - TZDs should not be used in patients with NYHA CHF class III or IV, and should be used very cautiously in patients with class II heart failure<sup>1,4,5</sup>

- The mechanism behind fluid retention with TZD use is not fully understood and is most likely multifactorial; however, it is hypothesized that TZDs reduce the renal excretion of sodium, leading to an increase in water retention and plasma volume<sup>7,8</sup>
  - Other hypotheses point to the so-called “vascular leak syndrome” that may occur with these agents which results in changes in plasma concentrations of vascular endothelial growth factor (VEGF) and increased vascular permeability.<sup>1</sup>

### ***Clinical Trials***<sup>9,10</sup>

- The results of a recent placebo-controlled randomized trial involving pioglitazone (PROactive study) with respect to cardiovascular risk demonstrated that after two years of pioglitazone therapy in high-risk DM II patients there was a 16% relative risk reduction in the combined end-point of time to death, MI, and stroke (p<0.05). However, there was an increased risk for symptoms of and hospitalization for heart failure in pioglitazone patients.
- The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study is a similarly designed ongoing trial that seeks to evaluate the cardiovascular effects of rosiglitazone. It is planned to be completed around 2009.

### ***Conclusions***<sup>6,7,11</sup>

- At this time there is insufficient information to recommend one TZD over the other; however, available data suggest that patients on TZD therapy should be monitored especially for the following:
  - ❑ Lipid abnormalities
    - Evaluate before initiation of therapy and 2-6 months later, or after switching agents, and then annually
  - ❑ Edema/CHF status
    - TZDs are contraindicated in NYHA CHF classes III or IV; use with caution in patients with class II heart failure and initiate at lowest possible dose and titrate gradually with careful monitoring; identify & treat exacerbations of CHF
    - Use with caution in patients also on insulin therapy

### **References**

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