

31 Glitazone Controversy: Is the Final Word Written?

Abstract: Glitazones entered therapeutic arena in 1990 with great expectations. However, the prototype, troglitazone was soon banned because of hepatotoxicity. Rosiglitazone and pioglitazone have been in extensive clinical use. ADOPT study showed superiority of rosiglitazone over metformin and glibenclamide in reducing the progression of type 2 diabetes. DREAM Study showed reduced risk of developing diabetes in subjects with impaired glucose tolerance with rosiglitazone therapy. However, these studies showed an increase in congestive heart failure. They also showed increased risk fractures in women. An alarm was raised by a meta-analysis of rosiglitazone studies by Nissen in June, 2007. The analysis revealed increased risk of myocardial infarction and cardiovascular deaths in the rosiglitazone-treated group. On the other hand an interim analysis of RECORD Study showed that cardiovascular end-points were not adverse in the rosiglitazone group.

These studies raise the following very important issues regarding drugs and their side effects, (1) Post-marketing surveillance of drugs in the long-term real-life situations. (2) Relationship of Pharma industry, regulatory authorities and medical profession. (3) Class effect of drugs. As most treating physicians are guided by simple ethical principles in this regard, they are most likely to discontinue use of rosiglitazone and proceed cautiously with the use of pioglitazone.

INTRODUCTION

Introduction of glitazones in clinical use in 1990 was viewed as a significant advance. The first drug to be introduced was troglitazone. It came with a bang and went out with a whimper. The drug was rated as a path-breaking discovery. In USA, where direct advertisement in lay press are allowed, patients on insulin were exhorted to check with their physicians whether they should take Troglitazone (Rezulin) to reduce their insulin requirement or even stop insulin therapy. The drug was about to enter phase three clinical trials in India when the FDA warning regarding its hepatotoxicity was issued. The drugs controller of India in its wisdom stopped the initiation of drug trials.

Troglitazone, although banned, continued to be attributed with a great potential in prevention of Type 2 diabetes. This is based upon the Troglitazone. In the prevention of diabetes (TRIPOD) study.¹ In this study, type 2 diabetic women with history of gestational diabetes were treated with troglitazone. There was 58% reduction in the development of diabetes in the treated group. Although troglitazone was stopped after 30 months of treatment, the incidence of emerging type 2 DM continued to be lowered 8 months after the cessation of treatment. It was postulated that the drug possessed a potential to prevent Type 2 diabetes.² More importantly, it appeared that the changes brought about by the drug have a memory effect for a long time. This information is forerunner of subsequent trials like DREAM (Diabetes Reduction assessment with Ramipril and Rosiglitazone Medication).³

ADOPT STUDY

This study evaluated and compared the efficacy of monotherapy with rosiglitazone, metformin and glibenclamide in a group of 4360, recently diagnosed Type 2 diabetic subjects.⁴ The end-point was progression of diabetes as judged by the failure of monotherapy (FBG:180mg/dl). Rosiglitazone was shown to be more effective than glibenclamide or metformin. At 5 years, the incidence of failure was 15%, 21% and 34% with rosiglitazone, metformin and glibenclamide respectively. A few secondary end points like amelioration of insulin resistance and beta cells preservation were also favorable in the rosiglitazone group.

A few disturbing side effects were noted in the rosiglitazone group. The edema and weight gain were known side effects of drug, documented again in this study. A few more side effects emerged; occasional congestive heart failure and increased LDL- cholesterol. The most intriguing side effects was higher rate of fractures in women.

DREAM STUDY

This study was conducted on 5269 subjects with impaired glucose tolerance or impaired fasting blood glucose.³ The 4 study arms were: rosiglitazone arm, ramipril arm, rosiglitazone plus ramipril arm and placebo arm. The end point was development of overt diabetes in each study arm. Rosiglitazone reduced the risk of developing diabetes by 62%. Obese subjects and those with truncal obesity particularly benefitted from the drug.

The side effect of weight gain and edema were present, as expected. Additionally, an increased incidence of congestive heart failure was noted in the rosiglitazone treated group.

A meta analysis of 42 studies on rosiglitazone was made by Nissen and published in New England Journal of Medicine on June 14, 2007.⁵ The study data were derived from those submitted by GlaxoSmithkline to FDA while seeking approval for the marketing of rosiglitazone. Criteria for inclusion in meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone and the availability of outcome data for myocardial infarction and death from cardiovascular event. The analysis revealed relative risk of 1.43 (95% confidence interval, 1.03 to 1.98; P=0.03) for myocardial infarction and 1.64 (95% confidence interval, 0.98 to 2.74; P=0.06) for cardiovascular deaths in rosiglitazone group as compared to the control group. Most of these studies were of short duration. Additionally, they were not adjudicated for cardiovascular end point. It was not possible to construct Kaplan-Meier charts, as time- to- event data were not available. Notwithstanding these limitations, Nissen pointed out that treating physicians should be alert to the possibility of serious cardiovascular effects of rosiglitazone in Type 2 diabetes.

RECORD (Rosiglitazone Evaluated for Cardiac outcome and Regulation of Glycemia in Diabetes) study appeared to come to the rescue of rosiglitazone.⁶ The study was planned for 6 years but an interim analysis at 3.75 years was performed to look at these controversial issues. This study included 4447 subjects treated with rosiglitazone. The cardiovascular end point was 1.75 events per 100 patient-years in the rosiglitazone regimes and 1.76 event per 100 patient-years in the non-rosiglitazone regime.

Fundamental Issues in the Controversy

The controversy has been visited by a number of authors thereafter.^{7,8} In fact, it raises some very fundamental issues in drug studies. Is it justifiable to conduct meta-analysis on a group of disparate studies, where the end points are dissimilar, duration of some of the studies is short, and number of subjects in some of the studies are small?

The possibility of increased fracture risk is the most intriguing side effect brought out in the ADOPT study. It reminds one of a peculiar finding in the UKPDS study, wherein a group of type 2 diabetics, in whom metformin was added on failure of sulfonylurea therapy experienced a spurt of increased mortality.⁹ This is in the face of the fact that metformin started initially did not exhibit any such tendency and in fact, was the only drug that reduced the diabetes-related mortality in this study. There has never been a good explanation of this difference in add-on metformin therapy and initial metformin therapy and it has been described as an inexplicable phenomenon by the statisticians. Increased fracture risk with rosiglitazone remains similar phenomenon, until we find the effect of the drug on bone density in humans as well as experimental animals.

This controversy also brings out the hazards of comparing one study with another. The basic factors in patient selection like age, duration of diabetes and ethnicity of studied subjects may

produce entirely different responses. The peculiarities at one of the participating study center may alter the data significantly, as was observed in the University Group Diabetes Program (UGDP), in which tolbutamide related increased mortality was largely confined to one of the participating centers. Duration of study may have a great impact on the emergence of cardiovascular complications and as these drugs are intended to be used for a very long period, it is always preferable to have as long a study as is possible

This controversy also raised the issue of post-marketing surveillance of drugs. Furthermore the cost of drug development has to be balanced against safety issues. In order to predict long term complications, it is important to study a drug for 5-10 years in a large number of patients, thus causing cost escalation. On the other hand, any fast track marketing of drug is likely to overlook serious adverse effects.

This controversy also touched upon some important aspects of relationship between scientific community, lay-media and regulatory authorities. Although a warning regarding the cardiovascular effects of rosiglitazone was already introduced in the drug literature in Europe, the USFDA lagged behind in doing so. The alarm was first raised by Nissen's article in the New England Journal of Medicine. Is it improper for scientists to do so directly through the scientific journals without alerting the regulatory authorities in advance? Does this alarm the patients unduly? These issues will continue to be debated. Now the USFDA has directed the pharma industry to include a 'black box' warning in the rosiglitazone literature.

A very novel concept regarding end-points in drug-studies is also emerging now. Most investigators have regarded glycemic control as the central end-point in anti diabetic drug studies. It now appears that it may also be a surrogate end-point. One can now visualize a drug that may be very effective in producing glycemic control, but may not retard or may even aggravate the vascular and neurological complications of diabetes. Rosiglitazone is now viewed as one such drug, but many other existing and upcoming drugs may fall in this category.

Class Effect of Drugs

Another important issue is to decide whether the cardiovascular complications are a class-effect of glitazone group of drugs. It is accepted that dry cough is a class side effect and reno-protection a class-effect of ACE inhibitors. In case of glitazones, some of the desirable effects as well as side effects are not class effects.

The effect of rosiglitazone and pioglitazone are different on blood lipids. While rosiglitazone has been shown to raise the LDL-cholesterol, pioglitazone lowers the LDL-cholesterol. Pioglitazone may also lower triglycerides. Rare instances of hepatocellular injury have been described with the use of rosiglitazone, but not so with pioglitazone. On the other hand, as a class of drugs, most glitazones have demonstrated toxicity; a notable newer compound being muraglitazar, which showed more than double the increased mortality with myocardial infarction and strokes.¹⁰ Most of the 50 investigational PPAR- γ ligands in the past seven years have been rejected because of their toxicity. Pioglitazone however, appears to be a relatively safer drug, as brought out in the PRO active study. The primary end-point was reduced by 10% in this study (not significant) and death, myocardial infarct and strokes reduced significantly by 16%.¹¹

Rosiglitazone in the Balance

In the light of above discussion, what should be the current recommendation regarding the use of rosiglitazone? In many experimental and short-term studies the drug is known to reduce carotid intimo-medial thickness¹² or act favourably in post-angioplasty patients.¹³ However, it appears that the gold standard will be long term, large, multicentric, controlled, adequately powered, prospective studies with clearly indentifiable end-points. These are difficult to carry out and after the furore raised in the literature recently, the subjects enrolled for some studies like RECORD are opting out of the study. Going by the basic principle of "Do no harm", rosiglitazone may have

to be dropped from our therapeutic armamentarium. Whenever an alternative drug is available, a good approach is to abandon the use of any drug suspected to have harmful effects. It is indeed difficult to convince a patient that a drug described to be harmful in lay-media is not really harmful. The last word on rosiglitazone has not yet been said in the literature, but for the treating physicians, who are guided by some of the basic principles discussed above, the last word has already been heard.

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Multiple Choice Questions

1. **Glitazone least likely to produce hepatotoxicity is:**
 - A. Troglitazone
 - B. Pioglitazone
 - C. Rosiglitazone
 2. **The least likely side effect of glitazone therapy is:**
 - A. Edema
 - B. Weight gain
 - C. Sexual dysfunction
 3. **In case of dyslipidemia, the best oral agent to be prescribed in type 2 diabetes:**
 - A. Rosiglitazone
 - B. Glibenclamide
 - C. Pioglitazone
 4. **The following drug does not produce hypoglycemia when used as monotherapy:**
 - A. Pioglitazone
 - B. Glipizide
 - C. Repaglinide
 5. **The most potent cardiovascular risk factor is:**
 - A. HbA1c > 7 %
 - B. LDL cholesterol > 100
 - C. Blood pressure 180 systolic and 120 diastolic
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1. B 2. C 3. C 4. A 5. C