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Review

Putting the RECORD straight?

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ABSTRACT

Ever since the withdrawal of troglitazone, questions had been raised about the safety of the thiazolinediones, rosiglitazone and pioglitazone, which were available for clinical use with special emphasis on their safety in terms of cardiovascular morbidities and mortality. Even though the U.S. FDA was looking into this matter and had advised a black box warning about the cardiovascular safety of rosiglitazone, a meta-analysis published in 2007 by Nissen et al in the NEJM brought things to a head, by showing a significant increase in the risks for cardiovascular morbidity as well as morbidity with the use of rosiglitazone. It also refuted the possibility that this may be a class effect by showing the relative safety of pioglitazone. Home et al reported an interim analysis of their RECORD study which refuted many of the findings of the meta-analysis published by Nissen et al. In spite of the accepted shortcomings of the meta-analysis as well as the significant questions raised about the trials which were chosen for this analysis and importantly, the statistical methodology used, Psaty et al in an accompanying editorial accepted the findings of the meta-analysis and excoriated the FDA for its non-performance as far as taking adequate safety measures regarding rosiglitazone use. The ensuing fallout created a media furore with conspiracy theories amongst others taking center stage and scientific debate taking a backseat, leading to unnecessary panic and stress to patients already on rosiglitazone therapy. Amidst all this, words of sanity reiterated the need for a more calmer and considered approach, and that whilst asking that patients be told about the possibility of these risks, one should wait for the final publication of the RECORD study as well as other long term studies which would give a more balanced view of the controversy. The recent publication of the final RECORD results showed that whilst rosiglitazone did have a two fold increase in the risk for heart failure, there was no increase in the risk for other cardiovascular morbidities or cardiovascular mortality caused by the use of this drug itself. These findings too had its critics. Whilst one would hope that this will bring an end to the rosiglitazone controversy, allowing a saner perspective on the saga, and its place in clinical therapy, this remains to be seen.

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1. The controversy

We seem to thrive on controversies. Some necessary, some needless, some self-serving and possibly concocted. But there has to come a time when one needs to come to some sort of a consensus and put the controversy behind us. Will the publication of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study [1] allow us to get a proper perspective of the ongoing rosiglitazone controversy and let us to come to some sort of a consensus about the use, if any, of rosiglitazone in clinical practice and its proper place in our diabetes management.

Before we discuss this in more detail, it would be worthwhile to look back and realize that thiazolinediones and controversies seem to happen in tandem, more so than any other oral anti-diabetes agent.

2. The start of the thaizolinedione saga

This started way back in 1982.

Takeda was searching for a lipid lowering agent which would have a somewhat similar action to the fibrates. The result was ciglitazone, a clofibrate analogue [2]. Studies showed a glucose lowering effect and this was surprising as a drug which essentially acted on fat cells was lowering blood glucose levels! It did lead to a lot of interest which quickly died down as the drug was seen to be associated with severe hepatic toxicity [3,4].

But work did continue to find out how and why a lipid lowering agent could lower blood glucose levels. By the mid-1990s it became known that these drugs bind to a nuclear receptor, predominantly located in fat cells. This again was puzzling, begging an answer as to why blood glucose levels should be dependent in part on a drug which acted on the fat cell nuclear receptors. One of the theories floated around was that these drugs act indirectly via the glucose/fatty-acid cycle, thereby lowering free-fatty-acid levels and possibly increasing muscle cell sensitivity to insulin and thereby leading to a greater use of glucose by the muscle cells with resulting lower blood glucose levels [3–6].

3. Troglitazone

Troglitazone, which was the first clinically approved thiazolidinedione became available for clinical use in the U.S.A. in March, 1997. This was in spite of the fact that 48 of the 2510 patients taking part in a baseline safety study showed alanine transminase activities (ALT) greater than three times the upper limit of normal, as against 0.6% in the placebo group, with 20 of these patients having ALT levels over ten times the upper limit of normal and five of showing a 20-fold increase [7]. By November, 1997, there were 135 cases of serious hepatotoxicity and six deaths [7].

It became available in Europe in 1998, but was withdrawn within 6 weeks by the UK Medicines Control Agency stating that "the risks of troglitazone therapy outweigh the potential benefits" [8]. By the time it was withdrawn in March 2000, 60 patients had died as the result of liver damage, a further 10 had received liver transplants (3 deaths), 10 had recovered and the outcome of a further 10 was unknown. The incidence of troglitazone-induced acute liver failure has been estimated at between 1 in 8000 and 1 in 20 000 patients treated [9].

4. And then came rosiglitazone and pioglitazone

Whilst troglitazone was still available in the U.S.A., rosiglitazone closely followed by pioglitazone were introduced in 1999. It was felt that having an effect both on the beta cell function as well as insulin resistance [10–14] they would be ideal to manage the dysglycemia of diabetes with a glucose lowering effect which would be more durable than that seen with sulfonylureas [15–18]. Although there were still questions about their hepatotoxicity, it was felt that this could be managed through regular testing for liver function. Furthermore, the beneficial cardiometabolic effects of these drugs including improvement in insulin resistance, blood pressure, decrease in levels of microalbuminuria, reduction of visceral fat mass, decreased systemic inflammation, and improvement in biomarkers and surrogate outcomes associated with atherosclerosis such as hs-CRP and carotid intimal thickness [19–25] would outweigh the associated hemodilution, anemia, weight gain, edema, and possible increased risk for heart failure [3].

Questions were raised about the lack of any significant clinical information made available in the public domain which could allow the treating physicians to make informed decisions regarding the new drugs. Surprisingly, and one could question the physicians themselves, although the U.S.A. FDA would have to bear a large brunt of this criticism, rosiglitazone became one of the best selling drugs in the U.S. even in the absence of such clinical evidence. Pioglitazone was not far behind and even after 1 year of its coming into the market, this drug had not one peer-reviewed clinical publication outside Japan.

5. The rumbling starts

Soon, one could hear some rumbling about the cardiovascular safety of these drugs especially rosiglitazone.

Before the rumbling could change into thunder, the World Health Organization took cognizance and carried out an analysis in 2003 which showed that TZDs may increase the risk for cardiac disease [3]. In view of this, in 2005, GlaxoSmithKline (GSK) the makers of rosiglitazone presented the U.S. FDA a preliminary pooled analysis which admitted possible risk for ischemic cardiac events with rosiglitazone. The FDA's review of these and other data led to the first rosiglitazone label warnings about possible cardiac adverse effects other than heart failure, particularly in patients also receiving insulin [26]. In August 2006, the FDA received GlaxoSmithKline's formal analysis of 42 randomized trials along with data from a large observational study. The meta-analysis suggested a possible "31% increase in cardiac ischemic events with rosiglitazone," whereas the observational study showed no such increased risk [26,27].

In early spring, FDA staff called for prominent boxed warnings about the risk for heart failure and edema with peroxisome proliferator-activated receptor-γ agonists and requested a May meeting with GlaxoSmithKline to further discuss the "signal of cardiovascular ischemic events with rosiglitazone" [3]. They planned to take the issue of heart failure and ischemic events for both rosiglitazone and pioglitazone to an Advisory Committee meeting in late summer or early fall.

6. And then lightning struck!

In late May 2007, Nissen and Wolski [28] published a controversial meta-analysis that claimed that rosiglitazone increased the risk for myocardial infarction by about 43% and cardiovascular death by about 64%.

The FDA moved the date for the Advisory Committee meeting to July 30, 2007 and narrowed the focus of the meeting to the cardiovascular ischemic issue with rosiglitazone. Treatment in patients with type 2 diabetes mellitus. The joint committee, consisted of 24 experts in cardiovascular disease, epidemiology, biostatistics, and endocrinology. They looked closely at three independently conducted meta-analyses demonstrating an increase in the relative risk of myocardial infarction, angina, or sudden death among patients taking rosiglitazone (Table 1).