Rosiglitazone and the thiazolidinediones: The trials of doing trials

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See the next issue of* Diabetes & Primary Care *for exemplar cases in which healthcare professionals consider a variety of patients with regard to their treatment regimen, with a special focus on glitazones.

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The last few months have seen some dramatic changes and controversy around the use of the thiazolidinedione (TZD) class of drugs. New data have emerged recently from a variety of sources suggesting that the TZDs are associated with heart failure and certain types of fracture, while rosiglitazone, in particular, has been scrutinized for a possible increased risk of myocardial infarction (MI). These findings have been reported in peer-reviewed journals and in the general press, leaving primary care teams and patients concerned about the continued use of a class of drugs that has become widely used in general practice. Here, I examine the new evidence and attempt to provide some guidance and recommendations for primary care diabetes teams.

TZD history

The TZDs lower blood sugar, primarily by increasing insulin sensitivity in peripheral tissues via activation of peroxisome proliferator-activated receptors (PPARs; Vamecq and Latruffe, 1999). The first TZD, troglitazone, was withdrawn from the market in 1997 owing to liver toxicity. Although the TZDs currently on the market (rosiglitazone and pioglitazone) received their European licenses 7 years ago, they have only recently become widely used in primary care. There are now at least one million annual prescriptions written for these drugs in England alone (Kazi, 2007).

Associated risks

Both TZDs offer persistent glucose-lowering effects (Yki-Jarvinen, 2004), but what has caused concern is that new data reinforce the likelihood that both agents increase the risk of heart failure (Singh et al, 2007), probably through complex gene expression in the kidneys, which leads to fluid retention. Indeed, an interim analysis of the RECORD trial (Home et al, 2007), the DREAM trial (Gerstein et al, 2006) and the ADOPT trial (Khan et al, 2006) showed an increased risk of heart failure associated with rosiglitazone use. The PROActive study also showed a similar increased risk of heart failure associated with pioglitazone use (Dormandy et al, 2005).

A more recent finding relating to a safety issue with the TZDs is that of an increased risk of certain types of less common fractures. An animal model suggested that these agents can lead to diminished bone formation and death of osteogenic cells (Rzonca et al, 2004). The ADOPT study seemed to confirm this observation as it, surprisingly (according to the investigators), reported an increased rate of certain specific wrist fractures in women treated with rosiglitazone compared with the active comparator (Khan et al, 2006), and two further studies have shown an increased tendency, in both men and women, for TZD users to experience fractures (Grey et al, 2007; Yaturu et al, 2007).

The safety issue that has caused the biggest furore and most concern amongst primary care teams and patients is that of an apparent increased risk of MI and cardiovascular disease with rosiglitazone. This concern first emerged with the publication of a meta-analysis (Nissen and Wolski, 2007) comparing rosiglitazone with other therapies or placebo in 42 studies. A meta-analysis such as this can offer strength by including data from published and unpublished trials from 15 560 patients randomly assigned to rosiglitazone. This meta-analysis showed that rosiglitazone was associated with a significant increase in the risk of MI. Unfortunately, many of the studies assessed included clinical heterogeneous trials and these make the conclusions arrived at by the authors less than clear cut. Several editorials have added to the controversy (Psaty and Furberg, 2007; Editorial, 2007), most concluding that a small number of additional or fewer events could have altered the outcome reported in the meta-analysis; however, most commentators agreed there appears to be a signal for the cardiovascular toxicity of rosiglitazone.

The RECORD study

The controversy arising from this meta-analysis prompted an early, unplanned interim report from the RECORD study (Home et al, 2007). This study is a multicentre, open-label, non-inferiority study with the specific aim of measuring the

effect upon cardiovascular outcomes of treatment with rosiglitazone. This interim report, based on data at around the half-way point, revealed that although at planning the study was adequately powered, the event rate was much less than expected, and this, combined with the early analysis, weakened the overall power of the interim analysis. The lower event rate also may now mean that a definitive answer may not be found when the study is completed. It does, however, reinforce the heart failure risk.

What does this recent evidence questioning the safety of the TZDs mean for primary care teams in practice?

It is worth considering if there is any evidence for important differences between the two available TZDs in terms of cardiovascular risk. Unfortunately, head-to-head comparative studies are limited in their scope and validity. We know that in one study, the agents showed no difference in hypoglycaemic effects but demonstrated subtle differences in lipid profiling favouring pioglitazone (Goldberg et al, 2005). More recently, a study comparing TZDs suggested that rosiglitazone may increase cardiovascular risk whereas pioglitazone may reduce it (Gerrits and Bhattacharya, 2007). The PROactive study failed to reach its primary end point, but did show risk reduction in important secondary end points, including a composite of all-cause mortality, non-fatal MI and non-fatal stroke (Dormandy et al, 2005). These papers suggest there is some evidence to confirm the superiority of pioglitazone in cardiovascular risk management.

It is also important to consider the benefits of these agents in the context of other oral anti-diabetic agents. A recent Cochrane review (Richter et al, 2007) found no benefit for rosiglitazone over other hypoglycemic agents such as sulphonylureas or metformin, whilst highlighting the risks of heart failure, fractures and possible increased cardiovascular risk. Another review also reinforces this message (Bolen et al, 2007), suggesting that most oral agents (TZDs, metformin and repaglinide) improved glycaemic control to the same degree as sulphonylureas. Large, long-term comparative studies are needed to determine the comparative effects of oral diabetes agents on hard, clinical end points. We know that these sorts of comparative data are cited frequently by prescribing advisors who will soon be challenging our assumptions about hypoglycaemic therapy.

What should primary care teams do when considering the case for prescribing the TZDs?

The evidence we have so far shows that the only benefit that the TZDs have over other glycaemic agents is a more sustained effect on glycaemic control compared with sulphonylureas, but at a cost of increased heart failure, weight gain and fracture rate. This would appear to place them as third-line agents at best, when metformin or sulphonylureas fail, in keeping with current NICE and SIGN guidance. A revision of the NICE guidance is anticipated in early 2008 and could clarify this suggestion, but it is unlikely to alter the order in which these drugs are used. Recently, an advisory committee of the US FDA voted in favour of keeping rosiglitazone on the US market, but only for as long as the TZD class of drugs included 'boxed warnings' of heart failure (Rosen, 2007).

An important strength of primary care diabetes is the excellent and accurate databases that are held in general practice. Teams will have been searching their diabetes databases for associations between TZD use and heart failure and osteroporotic fractures and, in the case of rosiglitazone, ischaemic heart disease.

With events as significant as those described, there needs to be a forthright engagement with patients so that they can make an informed decision about these drugs and whether or not they fit with their individual patient-oriented outcomes and perceived needs. Many patients have been contacting practices already and team members will want to give a clear and consistent message. Faced with clear evidence and warnings, teams are likely to put safety first. In the light of this, it is difficult to envisage prescriptions of TZDs increasing and, in the case of rosiglitazone, prescriptions will almost certainly decline. In his detailed commentary on the TZDs, Rosen rightly points out many of the complexities when looking for cardiovascular outcomes with hypoglycaemic agents (Rosen, 2007). After this controversy subsides, 'the trials of doing diabetes trials' will remain great, with important gains from positive outcomes, and significant disadvantages with negative outcomes. ■

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