The final chapter in the rosiglitazone story

Colin Kenny

The European Medicines Agency (EMA) has recommended the Europe-wide suspension of the thiazolidinedione (TZD) rosiglitazone in all formulations (Avandia® and Avandamet® in the UK) (European Association for the Study of Diabetes, 2010). The withdrawal date for rosiglitazone has been brought forward and is now 21 October.

During the past few months, advisory subcommittees of the US Food and Drugs Administration (FDA) and EMA have been meeting to appraise new data on whether the risk of cardiovascular (CV) problems with rosiglitazone has a critical impact on its risk–benefit profile. FDA has made a number of recommendations to try to determine the safety of the drug and further restrict its use, without an outright ban at present (Woodcock et al, 2010).

The two TZDs, pioglitazone and rosiglitazone, have been available in the UK since 2000 and each have prominent roles in the majority of prescribing algorithms for type 2 diabetes. Over that time, a better understanding of the individual pharmacology of rosiglitazone and pioglitazone has emerged, and an explanation has unfolded on their different CV-risk profiles, in spite of belonging to the same drug class (Rosen, 2010).

NICE (2009) guidance recommends them as second- and third-line agents, as did the SIGN (2010) guidance – although SIGN distinguishes between the two agents, specifically stating that rosiglitazone should not be used in people with acute coronary syndrome or a history of myocardial infarction.

New data

Three years ago, Nissen and Wolski (2007) raised safety concerns about rosiglitazone with the publication of a meta-analysis suggesting that, compared with other treatments for diabetes, rosiglitazone was associated with a 43% higher risk of myocardial infarction (MI) (P=0.03) and a 64% higher risk of CV death (P=0.06).

Steve Nissen has remained trenchant in his criticism of the drug and recently published a revised meta-analysis including all randomised controlled trials of rosiglitazone of at least 24 weeks' duration that reported CV adverse events (Nissen and Wolski, 2010). This included 56 trials, involving 35 531 participants – 19 509 who received rosiglitazone and 16 022 who received control therapy. The analysis showed that rosiglitazone therapy significantly increased the risk of MI (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.02–1.63; P=0.04) but not CV mortality (OR, 1.03; 95% CI, 0.78–1.36; P=0.86). The authors concluded that these current findings suggest an unfavourable risk–benefit ratio for rosiglitazone, and the totality of randomised clinical trials continue to demonstrate increased risk for MI, although not for CV or all-cause mortality.

In addition to the Nissen and Wolski data, Graham et al (2010) reported the results of a large cohort study examining the risk of CV events in 227 571 people aged ≤65 years who were treated with rosiglitazone or pioglitazone. The authors found that, compared with pioglitazone, rosiglitazone was associated with an increased risk of adverse CV events, including heart failure and death. Another study included 91 521 people with diabetes whose data were retrospectively extracted from the UK General Practice Research Database (Tzoulaki et al, 2009). Pioglitazone was associated with a significant 31–39% lower risk of all-cause mortality compared with metformin monotherapy (P=0.02 to P<0.001). In contrast, people taking sulphonylurea monotherapy showed a significant 24–61% increased risk for all-cause mortality compared with those taking metformin monotherapy (P<0.001), and rosiglitazone was associated with a 34–41% higher risk of all-cause mortality compared with pioglitazone (P=0.14 to P=0.01).

These data appeared overwhelmingly negative for rosiglitazone. The only prospective trial looking at the CV risk of rosiglitazone has been the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) study, a non-inferiority open-label study with an unblinded design, which examined the

Colin Kenny is a GP in Dromore, County Down, Northern Ireland.

European Association for the Study of Diabetes (2010) Press release: Statement on withdrawal of Avandia (rosiglitazone) in Europe from the European Association for the Study of Diabetes (EASD). EASD, Brussels. Available at: http://bit.ly/c9bPnX (accessed 29.09.10)

Food and Drugs Administration (2010) Press release: FDA statement on Avandia TIDE trial. FDA, Silverspring, MD. Available at: http://bit.ly/9MXHsE (accessed 29.09.10)

Graham DJ, Ouellet-Hellstrom R, MaCurdy TE et al (2010) *JAMA* **304**: 411–18

Home PD, Pocock SJ, Beck-Nielsen H et al (2009) *Lancet* **373**: 2125–35

Kelley T (2010) Glaxo sees $2.4 billion legal charge in second quarter. *Bloomberg*. Available at: http://bit.ly/bD3oRv (accessed 29.09.10)

Nathan DM, Buse JB, Davidson MB et al (2009) *Diabetes Care* **32**: 193–203

NICE (2009) *Type 2 Diabetes: Newer Agents for Blood Glucose Control in Type 2 Diabetes.* NICE Clinical Guideline 87. NICE, London

Nissen SE, Wolski K (2007) *N Engl J Med* **356**: 2457–71

Nissen SE, Wolski K (2010) *Arch Intern Med* Jun 28 [Epub ahead of print]

Rosen CJ (2010) *N Engl J Med* **363**: 803–6

SIGN (2010) *116: Management of Diabetes. A National Clinical Guideline.* SIGN, Edinburgh

Tzoulaki I, Molokhia M, Curcin V et al (2009) *BMJ* **339**: b4731

Woodcock J, Sharfstein JM, Hamburg M (2010) *N Engl J Med* Sept 23. Available at: http://bit.ly/cvqTtd (accessed 29.09.10)

Yusef S (2010) The urgent need to use reliable methods to assess the true effects of glucose lowering drugs and other therapies on major cardiovascular outcomes. Available at: http://scr.bi/acrcvR (accessed 29.09.10)

addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes (Home et al, 2009). This study confirmed the increased risk of heart failure and of some fractures, mainly in women. The study was inconclusive about any possible effect on MI; rosiglitazone did not increase the risk of overall CV morbidity or mortality compared with standard blood glucose-lowering drugs. However, weaknesses in the trial have been observed, including a low event rate in a high-risk population of people with diabetes, a high loss to follow-up, and the open-label design of the study. FDA has decided to reappraise the study (Woodcock et al, 2010).

The only way to resolve these issues is a prospective study sufficiently powered to examine the different CV risks of both the TZDs. The TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) was planned to do this, and amid concerns about the trial's viability its principal investigater Yusuf (2010) wrote to the FDA committee offering his opinion that the small meta-analyses and observational analysis of databases could be extremely misleading in evaluating therapies. He advocated that reliable results can only be obtained by large long-term trials that accrue over 1000 (ideally several thousand) events.

FDA (2010) has since informed GlaxoSmithKline (GSK), the manufacturers of rosiglitazone, that the post-marketing TIDE has been placed on partial clinical hold. Yusef's plea to respect prospective controlled trials over uncontrolled retrospective studies goes some way to explaining why, in the case of the FDA subcommittee, 33 members of the joint advisory committee met for 20 hours over 2 days before agreeing that the drug posed significant CV risk. Twelve voted that it should be removed from the market, 10 voted for much stricter control over prescriptions, seven voted for further warnings, three believed no changes were necessary, and one abstained.

What does this mean?

First, there is no direct evidence that rosiglitazone prevents vascular events in people with diabetes. Second, emerging evidence suggests that rosiglitazone is less safe than pioglitazone. Third, a consensus document from the American Diabetes Association and EASD had already advised caution about the use of rosiglitazone (Nathan et al, 2009).

Those responsible for prescribing rosiglitazone in primary care will have moved quickly in the past 2 weeks – first to contact people taking rosiglitazone to reassure them, and then use the opportunity to review their medication and make appropriate switches and additions to it as needed. The Primary Care Diabetes Society has published guidance on this, available at: www.pcdsociety.org/statements. It would appear from prescribing trends that rosiglitazone was not being initiated de novo, although many people with diabetes have remained on the product and are presumably responding satisfactorily to it.

GSK has withdrawn marketing of rosiglitazone and are expected to record a £1.57 billion ($2.4 billion) charge in the second quarter to settle legal cases, including claims arising from the use of rosiglitazone (Kelley, 2010). However, it is worth noting that both TZDs were nearing the end of their drug patents, and as pioglitazone becomes available as a generic agent over the next 12 months, its acquisition costs will fall. Prescribing advisors will favour pioglitazone as a third-line agent over the more expensive emerging agents, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, especially as neither of these drug classes have long-term safety data.

Lessons learned

Rosiglitazone emerged at a time when there were few effective agents available to primary care diabetes teams, and it was welcomed as a novel agent. However, its effect was judged on its ability to lower HbA_{1c} and surrogate CV outcomes rather than patient-related outcomes. We should be demanding much more robust proof of CV safety before new drugs for type 2 diabetes are licensed. This is particularly the case where CV outcomes are more important than rigorous HbA_{1c} reductions.

Those of us working in primary care consider ourselves to be patient advocates and, as such, we should be recommending drugs for them that not only reduce the complications arising from the increased glycaemia associated with diabetes but also drugs that are safe and effective long-term. ■