Pioglitazone: Balancing risks and benefits

Data have become available suggesting a small increased risk of bladder cancer with pioglitazone-containing products and the European Medicines Agency (EMA) has published new guidance on the drug (EMA, 2011). The EMA's Committee for Medicinal Products for Human Use (CHMP) reviewed all published and unpublished data and confirmed that medicines containing pioglitazone "remain a valid treatment option for certain patients with type 2 diabetes, but that there is a small increased risk of bladder cancer in patients taking these medicines" (EMA, 2011). As a result, there have been changes to the product information for these drugs (Baum, 2011; *Box 1*). This editorial will look at what prompted this guidance change and the overall risks and benefits of pioglitazone.

Bladder cancer and pioglitazone

In preclinical studies, male rats treated with pioglitazone developed more bladder tumours than those treated with placebo (Electronic Medicines Compendium, 2010). The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study, which looked at the use of pioglitazone to reduce macrovascular morbidity and mortality in people with type 2 diabetes, reported more bladder tumours in the group receiving pioglitazone (11 versus four) but the number of confounding factors and timeframe of the study meant that it was not possible to attribute the tumours to pioglitazone treatment (Dormandy et al, 2005). Publication of data from a 4-year observational follow-up of this study is awaited.

In 2003, the US Food and Drug Administration (FDA) asked the manufacturers of pioglitazone to conduct a safety study to assess whether treatment with the drug increases the risk of bladder cancer. A Kaiser Permanente Northern California (KPNC) cohort study was designed to investigate the association. This study is being conducted over 10 years, and the results of a planned midpoint interim analysis have been reported (Lewis et al, 2011).

Individuals with any use of pioglitazone had an unadjusted bladder cancer incidence of 81.5 cases per 100 000 person years compared

Box 1. Key changes to the product information for pioglitazone (adapted from the manufacturer's communication to healthcare professionals; Baum, 2011).

- Use of pioglitazone is now contraindicated in people with:
  - Current active bladder cancer.
  - A history of bladder cancer.
  - Uninvestigated macroscopic haematuria.
- Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. Any unexplained macroscopic haematuria should be investigated before starting pioglitazone therapy (for full list of risk factors see Baum (2011); full product information is available at http://bit.ly/nazUB1).
- People with diabetes should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.
- In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully before initiating treatment in the elderly.
- After initiation of pioglitazone therapy, patients should be reviewed after 3–6 months to assess adequacy of response to treatment. Maintained benefits should be confirmed at subsequent routine reviews.

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with 68.8 for people who had never used pioglitazone (fully adjusted hazard ratio 1.2, 95% confidence interval 0.9–1.5). The authors concluded that short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for greater than 2 years was weakly associated with increased risk (Lewis et al, 2011). The FDA responded to the publication of this study by placing increased licensing restrictions on the drug – similar to those subsequently applied by the EMA – specifically advising healthcare professionals not to use pioglitazone in people with active bladder cancer and to use it with caution in people with a prior history of bladder cancer (FDA, 2011).

The French Health Products Safety Agency (Agence Française de Sécurité Sanitaire des Produits de Santé, 2011) has decided to withdraw the marketing authorisation of pioglitazone in France following the presentation of an, as yet, unpublished study. The study (available in French at: http://bit.ly/oRhbNW) needs to be peer-reviewed and published, but it would appear to be a retrospective analysis, which is reported as showing an increased incidence of bladder tumours in male pioglitazone users.

After reviewing data such as those above, the CHMP has asked the marketing authorisation holder to conduct an epidemiological study focusing on the characterisation of the risk of bladder cancer, with a particular focus on the risk period and risk with increasing age, to inform the evidence base for risk minimisation measures (EMA, 2011).

Cardiovascular disease and pioglitazone

But, what about the overall risk–benefit balance with pioglitazone? Although emerging data suggest that people with type 2 diabetes have an increased risk of cancer both from the condition itself, and, more controversially, from some of the treatments (Giovannucci et al, 2010), the greatest risk of premature death in diabetes is from cardiovascular disease. Out of all oral antidiabetes drugs, metformin carries the lowest risk of cancer when used as monotherapy (Currie et al, 2009) and evidence suggests that it may contribute to a reduction in cardiovascular disease risk (Holman et al, 2008). In the PROactive study, subgroup analyses showed a reduction in death, myocardial infarction and stroke (Dormandy et al, 2005). Pioglitazone has also been shown to significantly reduce the risk of recurrent stroke in high-risk individuals (Wilcox et al, 2007) and the risk of myocardial infarction or acute coronary syndrome (Erdmann et al, 2007).

Inevitably, pioglitazone is compared with the now withdrawn rosiglitazone. Both drugs have overlapping side-effects of fluid retention, heart failure and fractures, and a meta-analysis of rosiglitazone trials raised concerns of cardiovascular harm (Nissen and Wolski, 2010). However, a similar meta-analysis of pioglitazone trials showed that this drug was associated with a significantly lower risk of death, myocardial infarction or stroke than would be expected in a diverse population with diabetes (Lincoff et al, 2007). A retrospective cohort study using the UK general practice research database also suggested that pioglitazone was associated with the lowest all-cause mortality among the oral antidiabetes agents (Tzoulaki et al, 2009). This favourable cardiovascular risk profile highlights the importance of pioglitazone as a treatment option for people with type 2 diabetes.

Conclusions

With clarification of the risks and benefits of therapy with pioglitazone, primary care prescribers will have to make decisions on the place of this last remaining drug in the thiazolidinedione class. It is important that individuals with diabetes, and their healthcare professionals, make well-informed choices. Although there is clear guidance from NICE (2009) and SIGN (2010) as to when to start the drug, as well as licences for single, double, and triple therapy and for use in combination with insulin, other factors need to be taken into consideration.

With this in mind, the Primary Care Diabetes Society committee has provided guidance (see page 202). Interestingly, at the time the EMA was deliberating about pioglitazone, it also approved generic versions of the drug (EMA, 2011). With its large evidence base, known risks from extensive research, and increasing cost-effectiveness, it is likely that pioglitazone will continue to be widely prescribed. ■