Pioglitazone and bladder cancer

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we focus on the 5-year outcomes of a study into the relationship between pioglitazone and bladder cancer following the introduction of new guidance for pioglitazone by the European Medicines Agency.

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In preclinical studies, male rats treated with pioglitazone developed more bladder tumours than those treated with placebo (electronic Medicines Compendium, 2011). The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study reported a non-significant excess of bladder tumours among people treated with pioglitazone (Dormandy et al, 2005). A 4-year observational follow-up of this study is ongoing and publication of data is awaited.

Following these concerns, the US Food and Drug Administration (FDA) requested that a safety study be conduced to assess whether treatment with pioglitazone increases the risk of bladder cancer (Lewis et al, 2011; summarised alongside and overpage). A Kaiser Permanente Northern California cohort study was designed to investigate this question over the course of 10 years, and the results of a planned midpoint interim analysis have now been reported and are summarised here (Lewis et al, 2011).

The authors of this study concluded that short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for >2 years was weakly associated with increased risk. Absolute risk would appear to be small. The authors confirmed that the study will continue as planned to more precisely assess the relationship between longer-term pioglitazone use and bladder cancer risk. This study should be scrutinised carefully by healthcare professionals with an interest in diabetes care.

The French Medicines Agency (Afssaps) are leading the field with their decision to suspend the use of pioglitazone-containing medicines in France (European Medicines Agency [EMA], 2011a) following the presentation of study (as yet unpublished), which is available on online in manuscript form (Caisse nationale de l'assurance maladie, 2011; in French). It is a retrospective analysis that appears to show an increased incidence of bladder tumours in male pioglitazone users. This French study remains to be peer reviewed and published.

Does Lewis et al's (2011) cohort reflect a typical UK population? The study is prospective with predefined outcomes, well controlled, and carefully matched to a cancer register. The cohort differs from most of the UK NHS population by having a slightly higher socioeconomic status, although the large numbers involved may mitigate some of the effects of this confounder.

The EMA (2011b) have now published new guidance on pioglitazone use. The EMA's Committee for Medicinal Products for Human Use says that pioglitazone-containing medicines "remain a valid treatment option for certain patients with type 2 diabetes but ... there is a small increased risk of bladder cancer in patients taking these medicines". The agency goes on to advise prescribers not to use these medicines in people with current, or a history of, bladder cancer, uninvestigated macroscopic haematuria, and to assess the risk of bladder cancer in the individual before undertaking pioglitazone treatment. They further advise follow-up within 3–6 months of initiation to ensure efficacy.

Caisse nationale de l'assurance maladie (2011) "Risque de cancer de la vessie chez les personnes diabétiques traitées par pioglitazone en France : une étude de cohorte sur les données du SNIIRAM et du PMSI." Available at: http://bit.ly/mRR4jz (accessed 31.08.2011) [In French]

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**: 1279–89

electronic Medicines Compendium (2011) *Summary of Product Characteristics: Actos Tablets.* Available at: http://bit.ly/n4TTwX (accessed 31.08.2011)

European Medicines Agency (2011a) *Suspension of use of these medicines in France while Europe-wide review continues.* EMA, London. Available at: http://bit.ly/kMMUfl (accessed 31.08.2011)

European Medicines Agency (2011b) *European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer.* EMA, London. Available at: http://bit.ly/nHTwGH (accessed 31.08.2011)

Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study

Lewis JD, Ferrara A, Peng T et al (2011) *Diabetes Care* **34**: 916–22

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Pioglitazone use of ≥2 years weakly associated with increased risk of bladder cancer

1 Some animal studies suggest a possible increased risk of bladder cancer with pioglitazone therapy and, in an ongoing cohort study undertaken at the request of the US Food and Drug Administration, the authors examined this association in a USA population.

2 The present study is an interim analysis of 5 years' data from 1 January 1997 to 30 April 2008.

3 Participants (n=193 099) were drawn from the Kaiser Permanente Northern California diabetes registry; all were ≥40 years of age between 1997 and 2002 and none had prior bladder cancer.

4 Treated as a time-dependent variable, use of each diabetes medication (defined as two or more

prescriptions within 6 months) was recorded and Cox regression-generated hazard ratios (HRs) compared pioglitazone use with non-pioglitazone use

5 Adjustment for cofounders (i.e. age, sex, race/ethnicity, diabetes medications, HbA_{1c}, heart failure, household income, renal function, other bladder conditions, smoking) was undertaken.

6 Those treated with pioglitazone comprised 30 173 individuals and this group were less likely to be aged ≥70 years and were more likely to have a baseline HbA_{1c} level >10% (>86 mmol/mol) than participants who had never used pioglitazone.

7 Among those with any use of pioglitazone there were 90 cases of bladder cancer; 791 cases of bladder cancer among non-pioglitazone uses.

8 Overall, ever use of pioglitazone was not associated with risk of bladder cancer (HR, 1.2; 95% confidence interval [CI], 0.9–1.5); results were similar in men and women (test for interaction, P=0.8).

9 Among those who received >24 months of pioglitazone therapy there was a small increase in the risk of bladder cancer at 5 years of follow-up (HR, 1.4; 95% CI, 1.03–2.0).

10 The authors of this interim analysis of data on the risk of bladder cancer among those who have received pioglitazone therapy for the management of hyperglycaemia concluded that short-term use of the agent was not associated with an increased incidence of bladder cancer, but that use for more than 2 years was weakly associated with increased risk.

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Following the withdrawal of rosiglitazone in 2010 due to cardiovascular safety concerns (European Medicines Agency [EMA], 2010), pioglitazone is the only thiazolidinedione indicated for use in people with type 2 diabetes as monotherapy, dual and triple combination therapy, and in combination with insulin (electronic Medicines Compendium, 2011) in the UK.

While there is some evidence of a potential cardiovascular benefit associated with pioglitazone (Dormandy et al, 2005), a variety of safety issues have been identified in relation to pioglitazone. Most recently, concerns linking pioglitazone to an increased risk of bladder cancer have emerged (US Food and Drug Administration [FDA], 2010). Fourteen bladder cancers (representing a frequency of 0.5%) occurred in the pioglitazone arm of the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study versus six in the placebo arm (representing a frequency of 0.2%; Dormandy et al, 2009).

In the study summarised here (Lewis et al, 2011) the authors reported on the potential link between pioglitazone and bladder cancer. The results showed that – after adjusting for cofounders – there was no significant increase in the risk of bladder cancer in people ever exposed to pioglitazone compared to those never exposed to pioglitazone. However, the risk of bladder cancer increased with increasing dose and duration of pioglitazone use. The FDA concluded from these data that pioglitazone therapy of a duration >12 months was associated with 27.5 excess cases of bladder cancer per 100000 person-years follow-up, compared with no use of pioglitazone (FDA, 2011).

Such observations have prompted the EMA (2011) to conduct a safety review of pioglitazone with respect to its link with bladder cancer. Following its review, the EMA's Committee for Medicinal Products for Human Use found that, although there is a small increased risk of bladder cancer among people taking pioglitazone-containing medicines, this increased risk can be reduced by appropriate patient selection and regular risk–benefit review.

Thus, although there appears to be a small increased risk of bladder cancer in association with pioglitazone, there is a clear need for further analysis of the types, evolution and severity of bladder cancer in people with diabetes who have received pioglitazone compared with those who have received other blood glucose-lowering agents. Accordingly, European regulators have asked for a pan-European epidemiological study to be conducted, focusing on more robust characterisation of the risk – in particular the risk period and risk with increasing age – to devise evidence-based approaches optimise the risk–benefit profile for pioglitazone therapy. In the meantime, robust clinical judgement and regular review are required to ensure that people with diabetes gain optimum benefit from pioglitazone-based blood glucose-lowering therapy.

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**: 1279–89

electronic Medicines Compendium (2011) *Summary of Product Characteristics: Actos Tablets.* Available at: http://bit.ly/n4TTwX (accessed 31.08.2011)

European Medicines Agency (2010) *European Medicines Agency update on ongoing benefit-risk review of Avandia, Avandamet and Avaglim.* EMA, London. EMA, London. Available at: http://bit.ly/bedySG (accessed 31.08.2011)

European Medicines Agency (2011) *European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer.* EMA, London. Available at: http://bit.ly/nHTwGH (accessed 31.08.2011)

US Food and Drug Administration (2010) *FDA reviewing preliminary safety information on Actos (pioglitazone).* FDA, Silverspring, MD. Available at: http://1.usa.gov/qaoUQa (accessed 31.08.2011)

US Food and Drug Administration (2011) *FDA drug safety communication: ongoing safety review of Actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure.* FDA, Silverspring, MD. Available at: http://1.usa.gov/p4NBZG (accessed 31.08.2011)