PROactive study

In John Dormandy and colleagues' PROactive study (Oct 8, p 1279),[1] there were imbalances in the incidence of certain tumours in patients randomly assigned the peroxisome-proliferator-activated receptor γ (PPAR γ) ligand, pioglitazone, that deserve attention. Dormandy and colleagues suggest that the marginally significant increase in bladder cancer in the group assigned pioglitazone was unlikely to be related to that drug. However, there are data to suggest otherwise.

Some studies in rodents suggest that PPAR γ ligands stimulate cancer formation.[2] Interestingly, bladder cancer was the only cancer seen in carcinogenicity studies in rats exposed to doses of pioglitazone equivalent to the maximum recommended human dose of 45 mg daily, based on surface area.[3] This was the dose of pioglitazone used in the PROactive study.

Those assigned pioglitazone in the PROactive study had a higher incidence of bladder cancer than those assigned placebo (eight *vs* 19 cases per 10 000 person-years). This finding is very important from a public-health perspective. Physicians must be diligent and fully investigate microscopic and gross haematuria in those taking pioglitazone. Additionally, caution is warranted when using pioglitazone in those with a history of bladder cancer.

I declare that I have no conflict of interest.

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1 Dormandy JA, Charbonnel B, Eckland DJA, et al, on behalf of the PROactive investigators. 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* 2005; **366:** 1279–89.

2 Koeffler HP. Peroxisome proliferator-activated receptor gamma and cancers. *Clin Cancer Res* 2003; **9:** 1–9.

3 Takeda Pharmaceuticals America. Actos package insert. Lincolnshire, IL: Takeda Pharmaceuticals America, 2004.

The results of PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study,[1] the first trial that aimed to assess the efficacy of glitazones in reducing cardiovascular events and mortality in type 2 diabetes mellitus, raise several questions and methodological concerns. Although the study is globally negative, a new "main secondary endpoint" appeared—ie, a new composite not described in the study protocol published in 2004. The conclusions of the study are based solely on this composite.

Other aspects of the results also need to be discussed. The results have not been adjusted for the determinants of coronary artery disease and stroke in type 2 diabetes revealed by the United Kingdom Prospective Diabetes Study (UKPDS).[2,3] Determinants of coronary artery disease include systolic blood pressure, glycosylated haemoglobin (HbA_{1c}), and LDL and HDL cholesterol.[2] Risk factors for stroke are age, male sex, hypertension, and atrial fibrillation.[3] The individual weights of these components have been calculated. A 1% decrease in mean HbA_{1c} concentrations over 10 years reduces diabetes-related death by 21%, myocardial infarction by 14%, stroke by 12%, and heart failure by 16%.[4] A median 10 mm Hg decrease in systolic blood pressure over 8·4 years reduces all-cause mortality, fatal and non-fatal myocardial infarction, and heart failure by 12% each.[5] The PROactive results should therefore be adjusted for the mean differences in HbA_{1c} (0·5%) and systolic blood pressure (3 mm Hg) recorded between the two groups. The opposite effects on lipid parameters seem to be directly related to the action of pioglitazone, and the results might not need to be adjusted for them. Further analysis of the PROactive study results is therefore required.

Finally, a major concern is the balance between the potential benefit of glitazones in preventing macrovascular complications in type 2 diabetes and an increased incidence (even unadjusted) of heart failure, as seen in the study.

Thus several questions remain, and the role of glitazones in the treatment of type 2 diabetes mellitus is not yet fully defined.

I have received fees for lectures and consultations from Eli Lilly, GlaxoSmithKline, Sanofi-Aventis, Servier, and Takeda.

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1 Dormandy JA, Charbonnel B, Eckland DJA, et al, on behalf of the PROactive investigators. 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* 2005; **366:** 1279–89.

2 Turner RC, Millns H, Neil HAV, et al. Risk factors for coronary artery disease in non-insulin-dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23). *BMJ* 1998; **316**: 823–28.

3 Davies TME, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus. United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med* 1999; **159:** 1097–103.

4 Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321:** 405–12.

5 Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000; **32:** 412–19.

On the basis of data from the PROactive study,[1] John Dormandy and colleagues conclude that "in patients with type 2 diabetes who are at high cardiovascular risk, pioglitazone improves cardiovascular outcome". Although we recognise that the study has been done according to well defined standards, we challenge this general conclusion.

The primary composite endpoint of the PROactive study consisted of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle. This endpoint is almost identical to the primary endpoint used in the Steno-2 study,[2] which showed a 20% absolute risk reduction and a 53% relative risk

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