Drug treatment in pre-diabetes

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the DREAM study – in which people with impaired fasting glucose or impaired glucose tolerance were given the thiazolidinedione rosiglitazone to increase the likelihood of regression to normoglycaemia.

Sudhesh Kumar, Professor of Medicine, Warwick Medical School

The DREAM study was designed to investigate in a prospective trial whether rosiglitazone can reduce the frequency of diabetes in those with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both.

The study screened 24 592 people at 191 sites worldwide and randomised 5269 of them with fasting glucose of 6.1–7.0 mmol/l and 2-hour plasma glucose concentration during an oral glucose tolerance test (OGTT) of <11.1 mmol/l. Fifty-eight per cent had IGT at baseline, 14 % had IFG and 28 % had both IGT and IFG. Subjects with any other cardiovascular risk factors were excluded. The study randomised subjects to ramipril or placebo and rosiglitazone (8 mg daily) or placebo in a 2-by-2 factorial design for 3 years.

Ramipril was not shown to have any significant effect on the onset of diabetes. Three hundred and six (11.6 %) of those on rosiglitazone developed diabetes or died compared with 686 (26.0 %) in the placebo arm. There was also a significant increase in those who reverted to normoglycaemia in the rosiglitazone group. Rosiglitazone treatment in this group of patients was associated with higher rates for heart failure (0.5 % versus 0.1 % in placebo). Rosiglitazone treated patients also showed a significant decrease in alanine aminotransferase.

These data were obtained whilst patients were still on treatment and therefore one has to be a little circumspect in interpreting the observed OGTT data. Further analysis of data obtained after a washout period would therefore be of interest. The subjects recruited excluded those with other cardiovascular risk factors, a somewhat unusual patient group in practice. The study was not powered to detect differences in cardiovascular events or other major clinical end points. The results of this study, whilst scientifically interesting, are unlikely to lead to a change in clinical practice.

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Des Spence, GP, Maryhill Health Centre, Glasgow

The study suggests that diabetes can be delayed with rosiglitazone in the pre-diabetes patient – sounds brilliant. But this is a huge leap of faith. There is no evidence that treating pre-diabetes prevents diabetic complications over the long term. The paper also suggests that pre-diabetes patients be treated in the same way as people with diabetes – so a whole new swath of the population become 'patients'.

Even if we assume that pre-diabetes is a true entity, for every one person who benefited, seven people took medication for 3 years with no benefit – the so called treatment paradox. Likewise, understand that the study reported [for rosiglitazone] no benefit in death or diabetes-related complications, caused an average 2.2 kg weight gain and significantly increased the risk of heart failure (despite the average age being 55 years).

Reflect on the opportunity cost. Rosiglitazone cost £1800 per patient – could this money be better spent on lifestyle modification, benefiting not merely the one in seven? Finally, if we are foolish enough to ride the 'pre-diabetes' bandwagon, then consider tried and tested metformin, with a comparable price of £75 per patient. This is no DREAM – I am about to start screaming!

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators (2006) *The Lancet* **368**: 1096–105

THE LANCET

Rosiglitazone for 3 years reduces the risk of developing type 2 diabetes

1 The aim of this study was to establish if rosiglitazone, a thiazolidinedione, prevents at-risk people from developing type 2 diabetes.

2 People over 30 years of age (n=5269) with impaired fasting glucose or impaired glucose tolerance or both were recruited.

3 People with a history of diabetes, cardiovascular disease and intolerance to either angiotensin converting enzymes inhibitors or thiazolidinediones were excluded.

4 Participants were recruited from 191 sites in 21 countries across five continents.

5 This study is part of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study. Participants received received rosiglitazone or placebo, and ramipril or placebo as part of a 2x2 factorial design. Only rosiglitazone versus placebo results are considered in this paper.

6 Participants were randomised to receive 8mg of rosiglitazone (n=2365) or placebo (n=2634). They were then followed for 3 years and the primary outcome was a composite of diabetes or death.

7 The composite endpoint of diabetes or death was reached by 306 participants (11.6 %) receiving rosiglitazone and 686 participants (26.0 %) receiving placebo (hazard ratio [HR] 0.40, 95 % confidence interval [CI] 0.35–0.46; $P<0.0001$).

8 The relative risk reduction for diabetes or death in people receiving rosiglitazone was 60 %. The absolute risk reduction was 14.4 %.

9 Normoglycaemia was achieved in 1330 participants (50.5 %) receiving rosiglitazone and 798 participants (30.3 %) receiving placebo (HR 1.71, 95 % CI 1.57–1.87; $P<0.0001$).

10 Adverse events were generally the same in both groups.

11 Heart failure developed in 14 participants (0.5 %) receiving rosiglitazone and two participants receiving placebo (0.1 %).

12 Mean bodyweight was increased by 2.2 kg more in the rosiglitazone group than in the placebo group ($P<0.0001$). In the rosiglitazone group, this was associated with a lower waist-to-hip ratio ($P<0.0001$).

13 Rosiglitazone at a dose of 8 mg per day for 3 years substantially reduces incident type 2 diabetes.

14 Rosiglitazone also increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance or both.

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

The DREAM study was a randomised controlled trial comparing the effects of rosiglitazone 8 mg daily, with ramipril 15 mg daily on progression from states of carbohydrate intolerance to frank type 2 diabetes, diagnosed on the basis of oral glucose tolerance testing.

The ramipril arm of the study demonstrated no significant effect on progression to type 2 diabetes (DREAM trial investigators, 2006), while there was around a 60 % reduction in incident type 2 diabetes or death with rosiglitazone. In particular, there were significant reductions in both fasting and post-prandial glucose levels associated with rosiglitazone which were maintained for the 4 year duration of the study.

Cardiovascular events were similar in both groups, although there was more reported heart failure in the rosiglitazone group. This observation is likely to be the consequence of fluid retention, rather than a function of left ventricular dysfunction *per se*, since a variety of smaller mechanistic studies have demonstrated improvement in cardiac function associated with glitazone therapy. An excess of heart failure was also reported in the other major glitazone outcome study to date, PROactive (Dormandy et al, 2005), again a likely function of fluid retention.

While more detailed evaluation of the heart failure adverse events for both these studies are awaited, it is however important to differentiate 'left ventricular dysfunction related' as opposed to the likely glitazone 'fluid retention mediated' heart failure, as the prognosis of both are markedly different.

'While this study may not directly affect practice in the UK, the glycaemic observations suggest that insulin sensitiser based oral hypoglycaemic therapy may influence the natural history of carbohydrate intolerance.'

While this study may not directly affect practice in the UK, the glycaemic observations suggest that insulin-sensitiser-based oral hypoglycaemic therapy may influence the natural history of carbohydrate intolerance resulting in durable glycaemic control, a concept to be further evaluated in the APODT study (Viberti et al, 2002).

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**(9493): 1279–89

The DREAM trial investigators (2006) Effect of ramipril on the incidence of diabetes. *New England Journal of Medicine* ***355***: 1551–62

Viberti G, Kahn SE, Greene DA et al (2002) A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* **25**(10): 1737–43

'Rosiglitazone increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.'