Glitazones to challenge metformin?

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 ADOPT study – in which the efficacy of a thiazolidinedione for maintaining long-term glycaemic control is investigated against other oral medications.

Mike Small, Consultant Diabetologist, Glasgow, Scotland

Having read the ADOPT study, Flora McSporran (aged 57 years, BMI 32 kg/m^2) has come to discuss what she should now do – after 3 months of dieting and exercising, she has still not achieved her glycaemic targets (HbA_{1c} now 7.7 % and she ate her personal trainer!).

While emphasising ongoing lifestyle modifications, I stress the role of evidence based medicine and the ADOPT double-blind RCT format with the key findings showing a 15 % failure on rosiglitazone compared to 21 % on metformin (to save confusion I ignore the sulphonylurea data). Flora points out that only 20 % of the original cohort were still taking drugs at 5 years, and that the difference in failure rate was less impressive when she reviewed the Kaplan-Meier estimates at Year 4 (the average duration of treatment). She asked if such studies usually have such a large drop-out rate (approximately 40 %), and I admit to this being disappointing and unusual, except for obesity studies.

I highlight the data showing better insulin sensitivity and a 9.8 mg/dl difference in fasting glucose, but she claims she can't get a feel for the homeostasis model assessment model, and that the difference in fasting glucose is actually only 0.5 mmol/l. She doesn't want to do blood glucose monitoring at home, and asks why the primary outcome results are not based on HbA_{1c}, since her friend told her that, in our solar system over the past 12 years or so, routine glycaemic management changes are based on the HbA_{1c} value. I point out that if we use rosiglitazone her HbA_{1c} would come down 0.13 % over 4 years and would result in an HbA_{1c} <7.6 %, and this would at least keep one healthcare professional happy! But she doesn't find this a persuasive argument.

By the time we discuss the average differences in weight between the treatments (7.8 kg), the 4 cm gain in waist circumference and the cost of her new wardrobe, I realise I'm in trouble. Worn down by her empowered approach, I am glad we didn't get to the doubling of risk for oedema and upper limb fracture, the possible need to increase her statin dose and the cost effectiveness of the drugs.

I start her on metformin (no change there then), arrange to see her again in 45 months time (the evidence based time to failure), pointing out that we could have delayed the next visit to 60 months if we had put her on rosiglitazone. I feel that it is important to admit that when she comes back to see me in about 4 years time, I really don't have a clue as to what we will add to her treatment – if health care is privatised by then, on a cost basis, she will end up taking a sulphonylurea.

Martin Hadley-Brown, GP, Thetford, Norfolk

We know that metformin and sulphonylureas are effective in improving glycaemic control in type 2 diabetes. Unfortunately their effectiveness diminishes with time and the proportion of patients achieving target HbA_{1c} levels progressively declines, probably as a result of continuing ß-cell failure. If the glitazones address issues of insulin resistance and slow ß-cell decline (though the latter point remains to be proven in humans) we might hope for longer lasting success with them.

From the beginning of the glitazone story I have eagerly awaited answers to two questions. First, would glitazones indeed show longer lasting glycaemic benefits than existing agents, and second, would they bring demonstrable reductions in morbidity and mortality?

The ADOPT study offers a reassuringly affirmative answer to my first question, and was not designed to answer the second. These results are good news for advocates of rosiglitazone and might reasonably encourage its increased use as a 'first-choice second-line' oral hypoglycaemic agent. Indeed its hypoglycaemic effectiveness actually outperformed that of metformin in the trial. However, it would require more convincing evidence of morbidity and mortality benefits for glitazones before they might threaten to supplant metformin as 'first-choice first-line' treatment.

Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy
Kahn SE, Haffner SM, Heise MA et al (2006)
New England Journal of Medicine **355**: 2427–43

Rosiglitazone reduces risk of monotherapy failure in type 2 diabetes

1 This study was carried out as part of A Diabetes Outcome Progression Trial (ADOPT) and aimed to investigate the long-term effects on glyceamic control of a thiazolidinedione versus a biguanide and sulphonylurea.

2 Under randomised, double-blind, controlled clinical conditions 4360 treatment naïve people with type 2 diabetes were allocated either 4 mg rosiglitazone, 500 mg metformin or 2.5 mg glyburide. Dosage was titrated up to the maximum daily effective dose (4 mg rosiglitazone BID, 1 g metformin BID or 7.5 mg glyburide BID).

3 The participants were monitored for time to failure of therapy, which was set at >180 mg plasma glucose per decilitre (10 mmol per litre) when fasting.

4 Participants were predominantly white, middle aged and obese. Median length of treatment was 4 years.

5 Versus metformin, rosiglitazone treatment resulted in a 32% risk reduction of monotherapy failure ($P<0.001$), and versus glyburide it inferred a 63% risk reduction ($P<0.001$).

6 Rosiglitazone and metformin treatment were shown to carry similar risks of cardiovascular events (3.4% versus 3.2%, respectively, P=NS) while glyburide treatment showed a significantly reduced risk of such events compared to rosiglitazone (1.8% versus 3.4%, respectively, $P<0.05$).

7 Rosiglitazone was associated with weight gain and oedema more frequently than in either of the comparator groups ($P\leq0.01$).

8 Serious hypoglycaemic events were reported on more occasions by participants in the glyburide group than the rosiglitazone group (557 events versus 142, respectively, $P\leq0.01$).

9 Compared to metformin, rosiglitazone treatment resulted in significantly fewer gastrointestinal side effects ($P\leq0.01$).

10 Further analysis of the data revealed the rate of fractures in female participants was higher in the rosiglitazone group (9.30%) compared to the metformin group (5.08%) and the glyburide group (3.47%). $P\leq0.05$ for the comparisons.

11 The evidence from this head-to-head trial suggests that rosiglitazone delays the progressive loss of glycaemic control associated with advancing type 2 diabetes for longer than metformin and glyburide.

12 The authors recommend that physicians consider the risk–benefit profile of each drug, in part elucidated in this study, when selecting an oral glucose-lowering medication for individual patients with type 2 diabetes.

Vinod Patel
Associate Professor, Warwick Medical School

ADOPT was a randomised controlled trial, comparing the effects of rosiglitazone, metformin or glibenclamide monotherapy in maintaining near-normal glycaemia in people with type 2 diabetes. The dosages used (rosiglitazone 4 mg BID, metformin 1 g BID, glibenclamide 7.5 mg BID) were reasonably high but clearly the results for the glibenclamide arm are difficult to interpret as we do not use glibenclamide to any great extent in the UK. However, this was a large study consisting: 4360 people. A Kaplan-Meier analysis showed that the incidence of monotherapy failure at a median of 4 years was 15% with rosiglitazone, 21% with metformin and 34% with glibenclamide. The definition of monotherapy failure was a fasting glucose level of greater than 10 mmol/l after at least 6 weeks of treatment at the maximum or maximum tolerated dose: this was the main primary endpoint.

The main result was that there is a 6% absolute risk reduction for the primary endpoint, comparing rosiglitazone with metformin, in favour of rosiglitazone. This equates to 66 treatment years with rosiglitazone to get one beneficial effect. This equates to over £40 000. Currently on cost economic grounds alone this would be cost ineffective.

Moreover, rosiglitazone was associated with more weight gain and more incidences of oedema than either metformin or glibenclamide but with fewer gastrointestinal side effects than metformin and less hypoglycaemia than glibenclamide. All these findings were statistically significant.

Where does this leave us for clinical practice? While there was some data showing that insulin sensitivity was a little more preserved with rosiglitazone in comparison to metformin. ß-cell function index was virtually the same across the three agents. Our current management paradigm of using metformin first line and then another agent such as a sulphonylurea or a thiazolidinedione will continue. One of the main concerns of our patients is weight gain and unfortunately the rosiglitazone arm was associated with weight gain. ADOPT was not designed to evaluate cardiovascular disease outcomes and these were actually found to be similar in the rosiglitazone and metformin groups but lower in the glibenclamide group. This finding differs from the UKPDS results, which showed that metformin reduces overall cardiovascular mortality and may reduce events. However, the duration of follow up was much shorter in the ADOPT study.

Overall the study suffered from the high rate of withdrawal of patients from each of the study arms but the overall conclusion must be that metformin remains, without any doubt the first-line treatment for people with type 2 diabetes.

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