Adopt, adapt, improve!

Eugene Hughes

Eugene Hughes is a GP, Isle of Wight, and Chair of Primary Care Diabetes Europe.

For the past 8 years, the management of hyperglycaemia in type 2 diabetes has been driven by the findings of the UK Prospective Diabetes Study (UKPDS, 1998). This landmark study influenced the positioning of existing therapies, putting metformin at the forefront with its beneficial effects on microvascular and, to some extent, macrovascular disease. Some commentators have drawn attention to the fact that this conclusion was based on a sub-group comprised of just over 300 people. Sulphonylureas (SUs) have settled into second place for most prescribers, but murmurings continue to be heard about cardiovascular safety.

Since the UKPDS 33 paper, there have been new therapeutic advances. Glitazones have been around for a few years, but their positioning is unclear, in part due to the technology appraisal from the National Institute for Health and Clinical Excellence (NICE, 2003) and a past lack of outcome data. However, the NICE guidance for glitazones is due to be reviewed in 2007. As both PROactive (Dormandy et al, 2005) and ADOPT (A Diabetes Outcome Progression Trial; Kahn et al, 2006) have been published since then, the NICE guidance looks to become redundant.

The question addressed by ADOPT was: 'what would have happened if the glitazones had been used as a treatment arm by the UKPDS?' The results were declared at the recent International Diabetes Federation congress in Cape Town, South Africa, and simultaneously published in the *New England Journal of Medicine* (Kahn et al, 2006).

The ADOPT study recruited 4300 newly diagnosed, treatment naïve people with type 2 diabetes, and followed them for 5 years. There were three treatment arms with almost identical numbers of participants randomised to metformin, rosiglitazone or glibenclamide (glyburide). The primary endpoint was time to monotherapy failure. Metformin and glibenclamide performed much as they did in the UKPDS: there was a sharp initial fall in fasting blood glucose and HbA_{1c}, followed by a progressive rise in their levels over time with a subsequent loss of glycaemic control. Of note was the greater initial fall in the rosiglitazone arm that was sustained such that at 4 years the HbA_{1c} was still below 7% without the need for a second agent. Indeed, the rosiglitazone curve looked as flat as Table Mountain (well, almost)!

Additionally, there were improvements in insulin sensitivity and an apparent stabilisation of beta-cell function in the rosiglitazone group. Cases of cardiologist-adjudicated heart failure were the same as in the metformin group, however a surprise finding was the increased fracture rate in women in the rosiglitazone arm. This may be an anomaly and requires further analysis.

Weight gain remains an issue. Over the course of the study those in the rosiglitazone arm gained significantly more weight than those in the metformin arm. Thus, the health equation of improved glycaemic control versus negative effects of weight gain needs to be examined.

With the diabetes-related drug market about to heat up with the arrival of the incretin mimetics and dipeptidyl peptidase 4 (DPP-IV) inhibitors, prescribing messages need to be clarified. So, what have we learned? ADOPT was a well-conducted study with carefully chosen outcome measures. The results are clear and unequivocal and should be considered when NICE guidelines are reviewed in the near future. These impressive data must surely pave the way for glitazones to usurp SUs and move into second place behind metformin.

As an ex-round table member, I am reminded of the motto: adopt, adapt, improve! It is time for us to examine the *ADOPT* data, *adapt* our prescribing habits, and *improve* the long-term glycaemic control of our patients with diabetes. ■

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