PROactive: More questions than answers?

Eugene Hughes

What does this study tell us about pioglitazone?

- When added to existing therapy in high-risk patients with type 2 diabetes, it significantly reduces the risk of heart attack, stroke or death.
- It delays progression to insulin therapy.
- It appears to be safe.

What does this study not tell us?

- Are the results applicable to rosiglitazone?
- Would the results have been different if all patients had been on a statin (as most observers would have expected)?
- Should we be using pioglitazone earlier in the disease process?
- Should we be using glitazones instead of sulphonylureas?
- Are the results applicable to 'lower-risk' individuals?

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The thiazolidinedione (glitazone/insulin sensitiser) class of drugs has been around for a few years now, but it had an inauspicious start. The first member of the class – troglitazone – was withdrawn soon after launch because of hepatotoxicity. The newer agents – rosiglitazone and pioglitazone – have so far shown themselves to be free of this complication.

The agents have managed to establish themselves as useful weapons in the arsenal of drugs needed to combat type 2 diabetes. Of particular interest has been the effects on various surrogate markers of the metabolic syndrome. Both drugs appear to have an impressive and sustained effect on glycaemic control: they have a modest effect on blood pressure; they reduce a raft of inflammatory markers such as plasminogen activator inhibitor-1; they have a beneficial effect on the lipid profile; and they reduce the progression of impaired glucose tolerance towards type 2 diabetes.

So, if they are so wonderful, why are they not used first line for all people with diabetes? Part of the answer may lie in the rather confusing positioning of the class of drugs in the National Institute for Health and Clinical Excellence (NICE; formerly the National Institute for Clinical Excellence) guidance (NICE; 2002). However, glitazone detractors have, until now, been able to trot out the time-worn defence: 'Where are the outcome studies?' They have argued that surrogate markers are one thing, but hard outcome data showing that these drugs demonstrate a significant reduction in cardiovascular morbidity and mortality would be the clincher.

Results were thus keenly awaited from the first of these outcome trials – the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, which was a prospective, randomised, double-blind, placebo-controlled, parallel-group study.

The PROactive trial has been described as 'brave', as over 5000 patients with type 2 diabetes and existing cardiovascular disease were recruited from 19 countries. They were randomised to placebo or a forced titration of pioglitazone up to a dose of 45 mg/day in addition to existing therapies. The primary end point was the time from randomisation to occurrence of a new macrovasular event or death. Secondary end points were individual components of the primary end point (such as non-fatal heart attack).

In Athens, on 12 September 2005, at the *European Association for the Study of Diabetes 41st Annual Meeting*, the diabetes world held its breath as the results of the PROactive trial were announced (www.proactive-results.com [accessed 28.09.2005]).

The results

The results could be perceived as being slightly disappointing. The primary end point showed a statistically non-significant 10 % risk reduction. The principal secondary end point (a composite of heart attack, stroke or death) did reach statistical significance, though, with a 16 % risk reduction. One of the reasons given for the difference was that the primary end point contained elements such as interventions (coronary artery bypass graft, for instance) that were physician-influenced rather than observational.

There were other interesting factors: only 50 % of this high-risk group were on statins, for example. There were no real safety concerns, but the pioglitazone group had an increase in fluid retention (there was a brisk debate – due to the method of recording, and the absence of echocardiography or BNP measurements – as to whether this amounted to 'heart failure'). The pioglitazone group demonstrated a delay in progression to insulin initiation.

Conclusion

The debate has only begun. Within the next 2–3 years, several other major studies will report (such as DREAM, ADOPT and RECORD). Hopefully, they will add much more to our knowledge of this fascinating group of drugs. In the meantime, I imagine that PROactive, despite all the hype, will bring about little change in prescribing habits in primary care, until the lessons are built into newer guidelines from agencies such as NICE. ■

National Institute for Clinical Excellence (NICE; 2002) *Management of type 2 diabetes – Managing blood glucose levels (Guideline G).* NICE, London