Rosiglitazone and pioglitazone – where do we go from here?

Sarah Jarvis

Author

Sarah Jarvis
General Practitioner

Richford Gate Medical Practice, Richford Gate Primary Care Centre, Richford Street, London, W6 7HY

Correspondence to:
Dr S Jarvis
(sarah.jarvis@gp-E85016.nhs.uk)

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In recent years, general practitioners (GPs) have been swamped by the burden of diabetes in the UK. The incidence has been growing almost as fast as our national waistlines, with the number of patients affected increasing from 800,000 to 1.8 million between 1980 and 2004, and the figure is predicted to increase to 3 million by 2010.

In addition, the landmark UK prospective diabetes study (UKPDS) has resulted in a gradual 'rebranding' of diabetes from a metabolic to a cardiometabolic disease. About 75–80% of patients with type 2 diabetes die, not from short-term complications of hyperglycaemia, but as a consequence of cardiovascular disease, which is more influenced by blood pressure and cholesterol management than by glycaemic control.[1-3]

Finally, far from being able to divert our energies from glycaemic control to tight control of blood pressure and cholesterol, we find glycaemic targets dropping ever lower. Poor glycaemic control is a major risk factor for microvascular complications, including diabetic retinopathy, peripheral neuropathy and nephropathy. While patients do not die of diabetic retinopathy, as the single most common cause of adult blindness it certainly causes huge morbidity. The burden of diabetic nephropathy is also increasing rapidly, with up to 45% of new cases of endstage renal failure accounted for by complications of diabetes.[4] It is against this background that the National Institute for Health and Clinical Excellence (NICE) recommends a target glycosylated haemoglobin (HbA_{1c}) of 6.5–7.5%, with a 6.5% target preferred, if feasible.[5]

The struggle to meet targets

GPs are struggling to meet these targets, with only 56–59% of patients achieving HbA_{1c} <7.5% in at least 50% of patients in 2004/5, and 59–62% of patients in 2005/6.[6] While metformin has an excellent safety and efficacy record, and continues to be standard first-line therapy for all patients who can tolerate it, UKPDS has shown us that for most patients, multiple hypoglycaemic agents are necessary.

Sulphonylureas are also well tried and tested, and relatively cheap, but carry the risk of weight gain and hypoglycaemia, especially with longer-acting versions such as chlorpropamide and glibenclamide. In addition, unlike metformin, they do not reduce the incidence of cardiovascular events.[3] What is more, many patients even on combination therapy with metformin and sulphonylureas do not maintain tight glycaemic control over time.[7]

The development of the glitazones was therefore welcomed by many as a useful tool in the battle for glycaemic control.

Increased cardiovascular risk?

In May 2007, alarm bells sounded with the publication of a meta-analysis of 42 trials using rosiglitazone, which suggested that rosiglitazone was associated with a statistically significant relative risk of myocardial infarction (MI) of 1.43 (95% confidence interval [CI] 1.03–1.98, p=0.03) and a relative risk of cardiovascular death of 1.64 (95% CI 0.98–2.74, p=0.06) – an increase of similar magnitude to that of MI, albeit statistically non-significant.[8]

Steve Nissen, the principal author, did not have access to all the trial data, but his conclusions raised enough concerns for the Food and Drug Administration (FDA) to convene a meeting of its Endocrinologic and Metabolic Drugs Advisory Committee, and Drug Safety and Risk Management Advisory Committee to discuss the issue. Eventually they concluded that "the use of rosiglitazone for the treatment of type 2 diabetes is associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylureas".[9] Despite this, the committee voted to recommend not that rosiglitazone be removed from the market, but that label warnings be added, educational efforts instituted and more research was recommended.[9]

The chair of the committee has been moved to justify this lack of definitive action.[9] He highlights the caveats inherent in the three independently conducted meta-analyses used, and the questions raised by the whole issue about the validity of surrogate end points. He also points to two large observational studies, which despite their limitations, have found in the case of rosiglitazone, no 'appreciable signal' of increased

cardiovascular risk. This, he suggests, may be a particular issue in the examination of events which are common, and whose rates are likely to be increased only slightly by a given drug.

There is an argument that on some occasions, surrogate end points are necessary to avoid the risk that new drugs will be denied to patients in need for many more years than might otherwise be the case. Cholesterol management is a case in point. The early statin studies were all placebo controlled, with dramatic reductions in cholesterol and cardiovascular events in relatively short time periods. Even in the last few years, it has been ethical to design studies such as the Heart Protection Study, in which patients with a history of cardiovascular disease were randomised to statin or placebo.[10] More recent studies, all of which are against active comparators, must be far longer, or far bigger (or both) in order to be powered to show benefits in outcome. It is interesting to note that ezetimibe has received limited approval by NICE on the basis that lowering of low-density lipoprotein (LDL) cholesterol, regardless of the method used to bring it about, results in reduced risk of cardiovascular events. The recently announced results of the ENHANCE study, which showed no significant difference in the surrogate end point carotid intimal media thickness (CIMT) with addition of ezetimibe to statin therapy will, no doubt, fuel the ongoing debate.[11]

Class effect?

The FDA investigation also alluded to the concept of class effects, and the difficulty in extrapolating both results and safety data. The chair of the committee stated "we are facing a troubling paradox: ... among the thiazolidinediones – a class of drugs that has been shown to improve metabolic control – rosiglitazone may increase cardiovascular risk whereas pioglitazone may reduce it".[9]

The clear reference by the FDA to a differentiation between pioglitazone and rosiglitazone was based on an observational study that revealed a 22% lower incidence of hospitalisation for acute MI among patients taking pioglitazone compared with rosiglitazone.[12]

This conclusion was bolstered further by a recent meta-analysis of pioglitazone data, which included 19 studies and 16,390 patients.[13] This meta-analysis showed an 18% relative risk reduction for the composite primary outcome of mortality, MI and stroke with pioglitazone treatment compared with the control group. The favourable effect of pioglitazone was consistent with different comparators (including placebo), in studies of patients with and without established cardiovascular disease, and in studies of short and long duration. Pioglitazone does have a much better impact on lipid profile than rosiglitazone[14] but it is unclear whether this alone is enough to account for the differences in cardiovascular risk.

The differentiation is further reflected in the European Medicines Agency ruling, that prescribing information for rosiglitazone (including combination preparations, such as Avandamet®) should be updated to include a warning that, in patients with ischaemic heart disease, rosiglitazone should only be used after careful evaluation of each patient's individual risk. The Agency ruled that no caveats were necessary for pioglitazone or for combinations containing pioglitazone.[15]

Action required

So where does that leave clinicians – and patients? In our practice, we have made a decision to actively change patients on rosiglitazone to pioglitazone. Both drugs have the same primary mechanism of action; both appear equally efficacious in reducing HbA_{1c}; but while the former appears to increase cardiovascular risk, at least in some patients, the latter appears to reduce it. In patients at such high risk of cardiovascular disease, this differentiation is crucial

Conflict of interest

SJ has received honoraria for sitting on advisory boards and lecturing from Takeda, Daiichi Sankyo and Servier.

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