Rosiglitazone — managing the change to a suitable alternative product

Now that rosiglitazone has had its product licence suspended clinicians will need to consider switching patients to alternative agents. Mark Peasley, clinical pharmacist at Aintree University Hospitals NHS Foundation Trust, provides some guidance.

Rosiglitazone has been under intense scrutiny since a meta-analysis in 2007 demonstrated a possible link between its usage and cardiovascular risk. This was added to existing concerns regarding rosiglitazone’s side effects: fluid retention, weight gain, increased fracture risk among postmenopausal women and worsening of lipid levels. Now that rosiglitazone has had its product licence suspended clinicians will need to consider switching patients to alternative agents.

National Institute for Health and Clinical Excellence guidelines issued in 2009 recommended that thiazolidinediones, such as rosiglitazone, should be used as a third-line agent (in combination with metformin and a sulphonylurea) or as a second-line agent when the patient is intolerant to or contraindicated from using metformin or sulphonylureas. Monotherapy should have only been considered when the patient cannot use either metformin or sulphonylureas and is not recommended by NICE.

Switching to pioglitazone?
The first thiazolidinedione to the market, troglitazone, was withdrawn in the UK in 1997 because of concerns regarding serious hepatotoxicity.

Troglitazone remained available in the US until March 2000. Its use in the US, its subsequent withdrawal and switching of patients to pioglitazone and rosiglitazone provides information and experience to clinicians regarding relative doses and side effects of the thiazolidinediones. The only alternative available, therefore, is pioglitazone.

Every 4mg of rosiglitazone is roughly equivalent to pioglitazone 30mg in HbA1c reduction. Rosiglitazone has a detrimental effect on lipid profiles whereas pioglitazone has a slight beneficial effect, including a reduction in total and low-density lipoprotein cholesterol levels. Patients on intensive statin therapy should therefore have their lipids monitored because they may be suitable for a reduction in statin dose once switched.

Pharmacists should be aware that although there is some favourable evidence for pioglitazone regarding cardiovascular risk (from the Proactive study), it is not free from side effects. Caution should be exercised when considering switching patients who are at risk of heart failure, those who have a high fracture risk and those for whom weight gain is particularly undesirable.

When considering alternatives other than pioglitazone, attention should be given to...
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licensed combinations, cautions and contraindications, side effects and glycaemic targets as well as individual patient preference.

Have they tried metformin?
Metformin is the first-line antidiabetic of choice with favourable effects on cardiovascular outcomes and weight without a significant hypoglycaemic risk. Only patients have been prescribed rosiglitazone in place of metformin (usually in combination with a sulphonylurea) there will normally be a good clinical reason.

Metformin is contraindicated in any patient with significant renal dysfunction (eGFR <30ml/min/1.73m²) or hepatic impairment because there is a risk of lactic acidosis. Depending on the reference source used, metformin is either cautioned or contraindicated in patients with heart failure, although it may be beneficial in these patients (patients with known heart failure should not have a thiazolidinedione).

Many patients are unable to tolerate metformin owing to gastrointestinal upset and, if not previously tried, modified-release metformin can be considered since it has a lower incidence of gastrointestinal side effects.

Can sulphonylureas be considered?
For patients not previously treated with sulphonylureas these can be considered, depending on the patient’s hypoglycaemia risk. Short-acting sulphonylureas are preferable, especially for elderly patients and those with renal impairment. All patients started on a sulphonylurea should be counselled on signs and symptoms as well as on how to manage hypoglycaemia appropriately.

What about the newer agents?
Dipeptidyl-peptidase-IV inhibitors (DPP-IV inhibitors) and glucagon-like peptide 1 agonists (GLP-1) may be indicated as alternatives to rosiglitazone. Glucose-insulinotropic peptide (GIP) and GLP-1 are gut-secreted hormones that have a role in glucose homeostasis. GLP-1 has been found to be deficient among patients with type 2 diabetes and it is the main therapeutic target (GIP levels remain relatively intact and there is a tachyphylaxis to its actions). GIP and GLP-1 exert many actions: they increase insulin release (in a glucose-dependent manner); they increase peripheral uptake of glucose, delay gastric emptying (thereby delaying glucose delivery); they inhibit post-prandial glucagon release (although hypoglycaemia-induced glucagon release is not affected); and they preserve pancreatic cell mass.

Exenatide and liraglutide are enzyme (DPP-IV) resistant GLP-1 agonists given by subcutaneous injection, the nonglucagon-like peptide (GIP) levels remain relatively intact and there is a shorter half-life and would require continuous intravenous infusion. The main side effects of GLP-1 agonists are nausea and gastrointestinal upset and both exenatide and liraglutide require upward titration from initial low dosing to improve tolerability. Exenatide is administered twice a day by subcutaneous injection. It has to be administered at least 60 minutes before a meal and should not be given immediately after a meal. Liraglutide is administered once daily and can be given at any time of day regardless of meal timings.

Although exenatide is licensed for use in dual therapy and triple therapy, liraglutide is only currently recommended as the third agent in triple therapy. When used alone the risk of hypoglycaemia with the GLP-1 agonists is low but this is increased when they are combined with sulphonylureas. If used in combination with a sulphonylurea a dose reduction for the sulphonylurea should be considered to reduce the risk of hypoglycaemia. Exenatide and liraglutide have been associated with the development of pancreatitis (although pancreatitis risk is higher among patients with type 2 diabetes) and caution should be exercised with exenatide in patients with significant alcohol history or gall bladder disease (both of which increase pancreatitis risk).

GLP-1 agonists should only be considered for patients with a body mass index of 35 or over, unless the only other alternative is insulin, where the addition of insulin would have significant occupational consequences or where weight loss would benefit other comorbidities (eg, significant cardiovascular disease). GLP-1 agonists should only be continued if HbA1c levels drop by ≥1 per cent and result in a weight loss of at least 3 per cent after six months. However, it is important to consider the effect of stopping rosiglitazone on HbA1c and consider using a target of 1 per cent drop from baseline (ie, before starting rosiglitazone). Cessation of rosiglitazone can lead to a reduction in fluid retention so patients who only just manage a 3 per cent weight loss should be reviewed carefully when considering their response to GLP-1 agonists.

Sitagliptin, saxagliptin and vildagliptin are orally active inhibitors of DPP-IV and increase endogenous GLP-1 (as well as GIP) levels. Saxagliptin and vildagliptin are only currently licensed in dual therapy regimens with metformin, sulphonylurea or pioglitazone, whereas sitagliptin is licensed in triple therapy regimens. Since these agents are weight neutral they may be preferable to pioglitazone, especially in patients for whom further weight gain is undesirable.

DPP-IV inhibitors should only be continued if a reduction in HbA1c levels of at least 0.5 per cent is seen in six months, although this target should be lowered in patients swapped over from rosiglitazone and it may be more appropriate to aim for a continued reduction of HbA1c level from baseline (ie, before the addition of rosiglitazone).

Should insulin be used?
For a few patients it might be necessary to substitute insulin therapy when rosiglitazone is withdrawn. This will require intense educational support and may have adverse consequences for the patient’s occupation, owing to the risk of hypoglycaemia. Once daily (using long-acting or intermediate insulins) and twice-daily regimens (using intermediate or biphasic insulins) are the most popular for use in patients with type 2 diabetes.

What about patients currently using insulin and rosiglitazone?
Patients may rarely be on combinations of rosiglitazone and insulin although this combination is not recommended owing to the increased risk of fluid retention and development of heart failure. Because of insulin resistance, discontinuation of rosiglitazone may require an increase in insulin dose if no additional agents are added.

Substitution of rosiglitazone with pioglitazone in these patients, although licensed, may still carry an increased risk of fluid retention, weight gain and development of heart failure. Combinations including a sulphonylurea with insulin will increase hypoglycaemic risk and may necessitate a reduction in insulin dose. Combinations of the GLP-1 agonists and insulin are currently unlicensed, although they are supported by some limited trial data. If a GLP-1 agonist is used the insulin dosage will normally require reduction. Sitagliptin is licensed for use with insulin and this may allow a reduction in insulin dose.

Will change in therapy affect driving entitlements?
In terms of therapy, drivers of cars and motorcycles with type 2 diabetes only need to inform the Driver and Vehicle Licensing Agency if they are treated with insulin, suffer from severe hypoglycaemic episodes or have loss of hypoglycaemia awareness.

Drivers of large goods vehicles (LGVs) and passenger carrying vehicles (PCVs) should have informed the DVLA if they are being treated with any oral hypoglycaemic drugs. LGV and PCV drivers will have their licence revoked if they become insulin treated and this will clearly have an impact on choice of therapy. Although use of sulphonylurea will not further affect driving entitlement, drivers should be advised of the need for regularly blood sugar monitoring and should also be reminded of the importance of recognising the signs of hypoglycaemia as well as appropriate management. In patients for whom GLP-1 agonists or DPP-IV inhibitors are initiated drivers must inform the DVLA if this is in combination with a sulphonylurea.

Further information regarding driving and diabetes can be obtained from the DVLA website at www.dft.gov.uk/dvla.