Roger Gadsby

A licence change for the glitazones

On 2nd September 2003, the European Agency for the Evaluation of Medicinal Products (EMEA) announced licence changes for thiazolidinediones (glitazones; EMEA, 2003) The main change is that the new licence allows glitazones to be prescribed as monotherapy if metformin is contraindicated or not tolerated. This commentary discusses the role of glitazones in light of the altered licence.

Available glitazones

There are two glitazones available at present in the UK. Pioglitazone is available in 15, 30 and 45 mg tablets and the dose can be titrated up to 45 mg once daily in monotherapy and oral combination therapy. Rosiglitazone is available in 4 and 8 mg tablets. The dose can be titrated up to 8 mg daily in monotherapy and in combination with metformin, and up to 4 mg daily in combination with a sulphonylurea.

How do the glitazones work?

Glitazones have a completely different mode of action to any of the other tablet treatments that are available to lower glucose levels in type 2 diabetes. In simple terms, they reduce the body's resistance to the action of insulin, enabling the body to use the insulin it makes more efficiently. In slightly more complicated biochemical terms, they activate the nuclear peroxisome proliferator activated receptor-γ (PPAR-γ), which leads to the increased transcription of various proteins regulating glucose and lipid metabolism. These proteins amplify the postreceptor actions of insulin in the liver and peripheral tissues, which leads to improved glycaemic control with no increase in the endogenous secretion of insulin. There are much more detailed and complicated biochemical explanations of the action of the glitazones now available, but they are beyond the scope of this commentary.

Are two monthly liver function tests still required?

Troglitazone was the first glitazone to be released in the UK. It was then withdrawn within 6 weeks of its launch. Troglitazone was found to cause severe liver damage in a few patients and over 50 deaths occurred worldwide. Neither rosiglitazone nor pioglitazone have been shown to cause liver damage in their clinical trial programmes, and in their extensive use in many countries across the world since their launch.

The licensing authorities, however, have remained cautious and the new licence still recommends that liver function tests be done before treatment is started, and then at two monthly intervals for the first year, and periodically thereafter. The drugs should be stopped if liver enzymes rise to three times the upper limit of normal, or if jaundice is observed.

How does the new licence fit in with the NICE guidelines on glitazones?

NICE issued revised guidelines on the use of glitazones in August 2003 – 6 days before the revised EMEA licence was issued (NICE, 2003). The NICE guidelines were based on previous licence indications and therefore did not refer to the use of glitazones as monotherapy. The EMEA licence indications for the use of glitazones in dual therapy state that they can be used with metformin, particularly in overweight patients and with a sulphonylurea if metformin is contraindicated or not tolerated.

The NICE guideline restates the use of glitazones as second-line oral combination therapy added to either metformin or a sulphonylurea, only when a sulphonylurea-metformin combination cannot be used due to a contraindication or intolerance to either the sulphonylurea or metformin. The new licence renders the NICE guidelines out of date, and presumably means that NICE will need to update its guidelines in light of the new licence.

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How should glitazones be used in in light of the new license?

Sulphonylureas, metformin and the glitazones are all effective drugs at lowering blood glucose levels. In clinical trials, all these drugs reduce HbA_{1c} levels by similar amounts, often in the range 0.8–1.8%. So how do you decide which one to use in initial monotherapy?

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Metformin

The NICE guidelines on glycaemic control in type 2 diabetes recommend that metformin should be used as the initial monotherapy of choice in all people who are overweight, defined as a BMI greater than 25. It also states that metformin should be considered as initial monotherapy in those with a BMI under 25.

The basis for this strong recommendation to use metformin as the initial monotherapy of choice is that it is thought that metformin has the added value of reducing cardiovascular events in addition to its effect on blood glucose lowering. This view comes from data from the UKPDS research study, in which a group of obese people with newly diagnosed diabetes who were randomised to metformin had less adverse cardiovascular events than those given a sulphonylurea or insulin.

It has been suggested that this benefit may occur partly because metformin works by affecting the way that insulin is utilised in the body, rather than by stimulating the pancreas to release more insulin, which is the mechanism of action of the sulphonylurea group of drugs.

Metformin, however, causes side-effects in a number of people. Side-effects include gastrointestinal effects, such as abdominal pain, nausea, diarrhoea and flatulence, and the sensation of a metallic taste in the mouth. They can mean that up to 20% of people may find it impossible to take metformin.

Sulphonylureas

If someone is unable to take metformin, should they be offered a sulphonylurea or a glitazone as their initial monotherapy? Those favouring sulphonylureas might say that they are well-known drugs with few side-effects or contraindications. Sulphonylureas reliably and quickly reduce blood glucose levels, and are therefore particularly helpful if the person has symptoms attributable to hyperglycaemia. They are also relatively cheap. The problem is that they may cause weight gain, and in comparison to metformin do not reduce adverse cardiovascular events.

Glitazones

Those favouring the glitazone argue that by using a drug that is treating the underlying condition of insulin resistance, they are dealing with one of the main causes of type 2 diabetes. The best clinical marker of insulin resistance is obesity, and so the use of a glitazone in obese individuals is particularly appropriate. Some argue that by using a sulphonylurea all you are doing is stimulating more insulin release in a person who is insulin resistant, so that the hyperglycaemic effect may be blunted, and the risks of weight gain increased.

Glitazones also can have favourable effects on blood pressure and the abnormal lipid profiles associated with diabetes. Pioglitazone, for example, can lower cholesterol by 15% (Khan ME et al, 2002). It is hoped that these beneficial reductions in surrogate outcomes for coronary heart disease (CHD) will translate into reductions in CHD morbidity and mortality in the long term. CHD outcome studies using glitazones are currently in progress.

Glitazones are effective at lowering blood glucose, and hopefully will be shown to reduce adverse CHD outcomes like metformin. This is why many would choose glitazones for initial monotherapy in overweight people if metformin is contraindicated or not tolerated. It is also the reason that many would choose glitazones as the agent to be added to metformin for people who are overweight, once metformin monotherapy alone is insufficient to control glycaemia. The new licence indication for the glitazones allows the earlier use of these drugs in type 2 diabetes, and enlarges the choice of oral agents available to doctors in managing people with this common condition. ■

European Agency for the Evaluation of Medicinal Products (EMEA) www.emea.eu.int

Khan ME, St Peter JV, Xue JL A (2002) Prospective randomised comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* **25**: 708–11

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