Peer reviewed article

Treatment of type 2 diabetes with glitazones – first do no harm?

Glitazones are widely prescribed in the treatment of type 2 diabetes as monotherapy and in combination with metformin, sulfonylureas and insulin. Rosiglitazone and pioglitazone, the two glitazones currently marketed, account for 21% of oral antidiabetic drugs used in the USA. Glitazones exert their pharmacological effect by directly stimulating the nuclear peroxisome proliferator-activated receptor gamma (PPAR-g) and thereby bypassing the insulin signalling cascade, the main site of insulin resistance. By sensitising muscle, liver and adipose tissue, glitazones lower fasting and postprandial glucose levels and decrease free fatty acid and insulin concentrations [1]. Glitazones also have pleiotropic effects and lower plasma levels of inflammatory markers such as plasminogen-activator inhibitor type 1, C-reactive protein, interleukin-6 and matrix metalloproteinase 9 [2]. In clinical studies glitazones have been shown to defer the progression of newly diagnosed type 2 diabetes [3] and to lower HbA1c by 0.7–1.5 percentage points depending on the study population.

However, although the glycaemic efficacy of the glitazones is comparable to that of metformin or sulfonylureas, they are considerably more costly (recommended daily dose of pioglitazone [Actos®] CHF 3.71, rosiglitazone [Avandia®] CHF 2.68, metformin CHF 0.71, glimepirid CHF 0.84, gliclazid [Diamicron MR®] CHF 1.55, insulin glargine [Lantus®] or detemir [Levemir®] 1 U ~ CHF 0.07), and there are a wide and growing range of side effects. Weight gain of 3–5 kg and fluid retention are common on glitazone treatment, increasing the risk of heart failure and oedema especially when combined with insulin treatment. Glitazones are therefore contraindicated in patients with NYHA class III and IV heart failure, and should not be combined with insulin treatment. Contrary to the liver toxicitiy of troglitazone, the first glitazone marketed, transaminase levels rise in less than 1% of patients treated with rosiglitazone and pioglitazone. Glitazone effects on bone are reported in at least seven studies, indicating accelerated bone loss and an increased fracture rate, particularly in postmenopausal women, with the distal extremities as the predominant fracture site [4]. Glitazones increase HDL cholesterol levels, however, rosiglitazone also raises LDL cholesterol and total cholesterol levels. There appear to be very few drug interactions with glitazones, which may also be given in diabetic patients with mild to moderate renal insufficiency.

Major concerns about possible cardiovascular harm of rosiglitazone arose with the results of recently published studies reporting a significantly increased risk of congestive heart failure, myocardial infarction and death (odds ratio 1.60; confidence interval [CI] 1.21–2.10, p <0.001; 1.43; [CI] 1.03–1.98], p = 0.03; and 1.29; [CI] 1.02–1.62, p = 0.03 respectively) [5, 6]. On the basis of the data available pioglitazone appears not to increase the rate of cardiovascular events, but the reasons for this difference are not clear.

From the diabetologist's point of view three large scale prospective studies, the ACCORD [7], the ADVANCE [8] and the VADT [9] trial, investigating the effects of intensive glucose control on cardiovascular events in patients with type 2 diabetes, have published somewhat surprising and disappointing results. They unanimously reported no benefit from "better" HbA1c (6.4 vs. 7.5%, 6.4 vs. 7.0%, and 6.9 vs. 8.4% respectively) on rates of cardiovascular events (apart from a reduction in the incidence of nephropathy in the ADVANCE trial). On the other hand, the ACCORD trial was terminated after 3.5 years because of excess deaths in the intensively treated group. However, rosiglitazone was part of the intensive therapy in all patients in the VADT trial, and was prescribed to 92% of the intensively treated patients in the ACCORD trial (vs. 58% in the standard treatment group), and all the participants had long-standing diabetes mellitus (mean 8–11.5 years).

In this issue of SMW Brändle and coworkers report the results of a carefully designed study on the cost-effectiveness of pioglitazone treatment in Swiss patients with type 2 diabetes and a history of macrovascular disease [10]. On the basis of the results of the PROactive trial they calculate an incremental cost-effectiveness ratio for pioglitazone vs. placebo of CHF 42 274 per life-year gained and of CHF 60 596 per QALY gained. How are these results and the above-mentioned effects of glitazones to be translated into clinical practice?

First, antihyperglycaemic treatment of type 2 diabetes is most effective, and with ongoing benefit regarding micro- and macrovascular complications, when introduced as early as possible in the course of type 2 diabetes. This approach is supported by the recently published post-trial follow-up of UKPDS patients who had a sustained reduction of micro- and macrovascular endpoints after 10 years despite the loss of glycaemic differences from the conventionally treated patients [11].

Second, given the combination of multiple cardiovascular risk factors in patients with type 2 diabetes, multifactorial intervention is far more effective and recommendable than the solely glucocentric approach, as shown by the Steno-2 study reporting a significantly reduced death rate in patients with multiple drug combinations and behaviour modification (hazard ratio 0.54, [CI] 0.32–0.89, p = 0.02) [12].

Third, in the treatment of type 2 diabetes lifestyle changes and metformin are the first choice, given the convincing endpoint data and the cost-benefit ratio. If the target HbA1c is not reached the addition of sulfonylureas is the next step.

Fourth, what of glitazones for the treatment of type 2 diabetes? In my opinion there is no indication for rosiglitazone. Pioglitazone may be an alternative in patients with metformin intolerance or renal insufficiency who are unwilling to begin with insulin treatment.

Fifth, I suggest a rethink on the so-called "treatment failure" of oral antidiabetic drugs as the main indication for insulin treatment. The effectiveness, cost, and, apart from hypoglycaemia, almost total absence of side effects make insulin the ideal treatment for diabetes mellitus.

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