Choice of monotherapy in newly diagnosed Type 2 diabetic patients: clinical perspective of ADOPT

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A Diabetes Outcome Progression Trial (ADOPT) investigated the durability of the anti-hyperglycemic effects of rosiglitazone (RSG; maximum dose 4 mg twice daily), metformin (MET, maximum dose 1 g twice daily) and glyburide (or glibencamide [GB]; maximum dose 7.5 mg twice daily) in 4360 drug-naive patients with Type 2 diabetes mellitus. The therapeutic goal in the trial was a fasting plasma glucose level below 140 mg/dl (7.8 mmol/l) and the primary end point was the time from randomization to treatment failure, defined as an fasting plasma glucose above 180 mg/dl (10 mmol/l). The results showed a cumulative incidence of monotherapy failure at 5 years of 15% for RSG, 21% for MET and 34% for GB, equating to risk reductions in primary end point for RSG therapy of 32% relative to MET and 63% relative to GB ($p < 0.001$ for both comparisons). There were significant withdrawals from each of the study groups and when glycosylated hemoglobin was used as the measure of long-term glycemic control, the differences between groups were more modest. RSG also resulted in greater weight gain and, notably, a significantly increased fracture rate in the upper and lower limbs of women (9.3%) compared with MET (5.1%) and GB (3.5%). Overall, taking into account the modest glycemic benefit of RSG over MET, the cost difference between these treatments and safety concerns with RSG, MET remains the rational choice of initial treatment of Type 2 diabetes mellitus.

Keywords: durability of glycemic control, glibencamide, metformin, monotherapy, rosiglitazone, Type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS) remains the cornerstone epidemiological and drug treatment trial on which contemporary guidelines for treating Type 2 diabetes mellitus (T2DM) are based. At least two lessons from that study are relevant to the purpose of A Diabetes Outcome Progression Trial (ADOPT). First, progressive deterioration in glycemic control, due to cumulative pancreatic β-cell failure, is a pathophysiological signature of T2DM [1]. Second, after a variable 'honeymoon' period in which oral agents, such as biguanide, metformin, sulphonylurea, glibenclamide, and even injectable insulin, ameliorate hyperglycemia, the inexorable trajectory of deteriorating glycemic control is restored [1–4], resulting in a requirement in the longer term for multiple therapies [5].

In recognition of these failings, the advent, in the late 1990s, of the thiazolidinediones (TZDs) was greeted with much fanfare and an expectation that these new agents might provide a radical new treatment for T2DM. TZDs (rosiglitazone and pioglitazone) are insulin-sensitizing drugs that act via agonist actions at PPAR-γ, a nuclear transcription factor expressed in many human cells. By alleviating peripheral tissue insulin resistance, it was hypothesized that TZDs would reduce insulin secretary demand and thereby reduce the rate of β-cell failure and the inexorable progression of the disease. Also, the coincidental expression of PPAR-γ in the pancreas and in several cells that coordinate the inflammatory process (e.g., macrophages, T-cells and stellate cells), has stimulated speculation that TZDs may have additional beneficial direct and/or indirect actions that influence β-cell survival.

Several strands of evidence support the overarching hypothesis that TZDs are protective to the pancreas. First, early treatment of genetically susceptible rodents with TZDs prevents the rise in β-cell death, preserves islet morphology and prevents the development of diabetes [6,7]. Second, these laboratory findings have some key functional correlates in humans. Thus, TZDs significantly reduce the proinsulin-to-insulin ratio [8–10], improve glucose entrainment of insulin pulsatility [11], and reduce glucose-stimulated insulin secretion [12], suggesting improvements in glucose signaling at the β-cell membrane and overall β-cell 'health'. Moreover, TZD-induced improvements in calculated β-cell function have been reported in several studies [9,13–15].

Finally, evidence from both the Troglitazone/Pioglitazone In Prevention of Diabetes (TRIPOD/PIPOD) study in Hispanic women with previous gestational diabetes, and from the

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Diabetes Prevention Program (DPP), suggest an ability of TZDs to at least postpone the onset of T2DM in many high-risk subjects [16–18]. In the more recent Diabetes Reduction Assessment with ramapril and rosiglitazone Medication trial (DREAM), rosiglitazone substantially reduced incident T2DM over 3 years in a large cohort of subjects with impaired glucose tolerance, impaired fasting glucose or a combination of these metabolic abnormalities [19].

This accumulated evidence provides the platform for ADOPT, a study designed to compare the durability of antihyperglycemic effects of rosiglitazone, with the hitherto pillars of traditional therapy, metformin and glibenclamide.

Study design

ADOPT was a randomized, double-blind, parallel-group study, conducted for a median of 4 years between April 2000 and June 2006 in 4360 drug-naive T2DM patients aged 30–75 years (58% male), at 488 centers in the USA, Canada and Europe. Patients were predominantly white and obese (BMI: >30 kg/m^2). The objectives of the study, its design framework and the baseline characteristics of its T2DM patient population were published earlier [20,21].

Randomized patients, diagnosed within the previous 3 years, with a fasting plasma glucose (FPG) in the range of 126–180 mg/dl (7.0–10.0 mmol/l), were drawn from a pool of 6676 screened patients; 2316 of these were excluded for various reasons, though mostly (1754 patients) because they did not satisfy inclusion criteria. The therapeutic goal in the trial was an FPG under 140 mg/dl (7.8 mmol/l). Initial drug doses were rosiglitazone 4 mg, metformin 500 mg and glibenclamide 2.5 mg. Dose increases to meet the therapeutic goal were allowed up to a maximum of 4 mg twice daily for rosiglitazone, 1000 mg twice daily for metformin and 7.5 mg twice daily for glibenclamide.

The primary end point was the time from randomization to treatment failure, defined as an FPG over 180 mg/dl (10 mmol/l) on consecutive testing after at least 6 weeks at the maximum-dictated or maximum-tolerated dose of study drug. Patients were followed at intervals of 2 months for the first year, and then 3-monthly for the remaining 3 years. FPG and glycosylated haemoglobin (HbA1c) were measured at each visit and an oral glucose tolerance test, to determine β-cell function, was performed at 6-monthly intervals. To monitor hepatic safety, liver function tests were performed at each visit for the first year and then at 6-monthly intervals.

Overall, the trial was designed to provide 90% power to detect a hazard ratio of 0.70, that is a 30% risk reduction for the rosiglitazone group relative to the metformin or glibenclamide groups in the incidence of monotherapy failure using a two-group log-rank test at $p = 0.05$ (two-sided test, adjusted for two comparisons).

Results

The primary endpoint data from ADOPT were presented to a symposium at the International Diabetes Federation (IDF) meeting in Cape Town (December 2006) and simultaneously in printed format [22].

The first point to note is that the drop-out rate in this trial was high at approximately 40%, although the numbers of noncompleters and their demographic, anthropometric and metabolic characteristics were similar across groups.

As for the results, the primary outcome data broadly support the hypothesis that TZD monotherapy can, relative to metformin or glibenclamide monotherapy, change the trajectory of deteriorating glycemic control in T2DM, at least during the early years after diagnosis. Thus, Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% for rosiglitazone, 21% for metformin and 34% for glibenclamide. Relative to metformin, the risk reduction with rosiglitazone was 32% and 63% relative to glibenclamide ($p < 0.001$ for both comparisons). Similar differences (34% and 62%, respectively) were evident when 140 mg/dl (7.8 mmol/l) was employed as the glycemic threshold more relevant to contemporary clinical practice for adding a second drug.

However, when HbA1c was used as the measure of long-term glycemic control, the difference between rosiglitazone and metformin groups was less marked, although rosiglitazone was clearly superior to glibenclamide. At 4 years, only 40% of the 1456 patients in the rosiglitazone group had an HbA1c less than 7%, compared with 36% of 1454 patients in the metformin group ($p = 0.03$) and 26% of 1441 taking glibenclamide ($p < 0.001$). Relative to both comparators, rosiglitazone appeared particularly beneficial for glycemic control (as judged by FPG) in patients aged over 50 years and, relative to metformin, in those with a waist circumference greater than 110 cm. There was

also a tendency for women to be better controlled than men on rosiglitazone when compared with the other agents.

The explanation for the superior durability of rosiglitazone may well lie in its superior effect on peripheral insulin sensitivity. Glibenclamide scarcely influenced this parameter throughout 5 years, whereas metformin, and to a greater extent rosiglitazone, improved it progressively over time. These heterogeneous effects of the three agents were mirrored in the calculated annual rate of loss of β-cell function: 6.1% for glibenclamide, 3.1% for metformin and 2.0% for rosiglitazone. At the end of the study, absolute values of the homeostasis model assessment of percent ß-cell function (HOMA-β) were similar across groups, but the cumulative loss of β-cell function with glibenclamide from its secretagogue-related peak value at 6 months was striking and a clear illustration of why this drug loses its antihyperglycemic efficacy over a relatively short time in a substantial proportion of patients.

If these data provide succor to the TZD advocates, there is also some comfort for their detractors. For all drugs, it seems, there are trade-offs to be made against their perceived benefits. For TZDs, these are generally well-known and, to an extent, as visible in ADOPT as in other trials. Thus, rosiglitazone monotherapy elicited greater weight gain (4.8 kg over 5 years) than glibenclamide (1.6 kg), whilst metformin invoked a weight loss (2.9 kg) in the same time-frame. Some of the weight gain with TZDs is undoubtedly fluid-retention-related, reflected here by a significant fall in hematocrit, a higher edema rate (14.1 vs 7.2% with metformin and 8.5% with glibenclamide) and an increased use of loop diuretics. But rosiglitazone's adipogenic potential was also in evidence and reflected as an expansion of both waist and hip circumferences, though leading to little overall change in waist-to-hip ratio.

As expected, rosiglitazone also raised the levels of both high-density lipoprotein and low-density lipoprotein cholesterol modestly, the latter requiring an increased statin usage. Glibenclamide treatment raised the circulating triglyceride concentration slightly.

Gratifyingly, the prospect of an increased incidence of congestive heart failure (CHF) with rosiglitazone, which was reported in the recent DREAM trial [19], was largely discounted in ADOPT, the number of events being similar to that with metformin. Interestingly, glibenclamide treatment was associated with a lower incidence of both CHF and total cardiovascular disease-related events, perhaps indicative of a random distribution of the small number of events overall. Hospitalizations and deaths from any cause were similar across treatment groups.

Glibenclamide was associated with a 'trademark' higher rate of hypoglycemic episodes than the other agents whilst, also as expected, metformin exhibited a higher rate of gastrointestinal side effects.

Of some surprise in ADOPT was a post-scripted table recording a significantly increased fracture rate in the upper and lower limbs of women taking rosiglitazone (9.3 vs 5.08% for metformin and 3.47% for glibenclamide). This is the first time that this particular side effect of TZD therapy has been reported in a major trial.

Significance

ADOPT has dispelled any lingering doubts regarding the ability of a TZD to show superiority to either metformin or glibenclamide in changing the trajectory of deterioration of glycemic control in T2DM. These observations are consistent with other trials where a TZD at least postponed the transition to diabetes in high-risk cohorts [16–19]. ADOPT also reinforces the belief that this beneficial effect of TZDs is attributable to improved peripheral insulin sensitivity, leading to a reduced annual rate of loss of pancreatic β-cells.

Other data on the relative effects of rosiglitazone, metformin and glibenclamide on fasted levels of circulating C-peptide, proinsulin, insulin and the proinsulin-to-insulin ratio have yet to be published from this study. Furthermore, additional data are awaited for blood pressure, C-reactive protein (CRP) and urinary albumin that may also cast rosiglitazone in a favorable light, since earlier studies have shown the drug's benevolent action on these parameters [23,24].

Viewing the outcome of ADOPT through a different prism, the data endorse to a large extent the current primacy of metformin as first-choice treatment in T2DM, not least because it too improves peripheral insulin sensitivity over a prolonged period and reduces the rate of loss of β-cell function when compared with glibenclamide. Whether the additional prolongation of β-cell function and more durable glycemic control with rosiglitazone might justify its displacement of metformin as first-line treatment is debatable. There is no evidence here, for example, that rosiglitazone can arrest the disease process completely and, when durable glycemic control is judged via HbA1c, the difference in the proportion of patients with a 4-year HbA1c less than 7% is unremarkable (40% for rosiglitazone, 36% for metformin).

Furthermore, the side-effect profile of rosiglitazone and the other TZD, pioglitazone, provides the skeptic with considerable ammunition. As well as weight gain, fluid retention, peripheral edema and perhaps a rather more distant potential for macular edema and CHF, the emergent effect on fracture risk in women is discouraging and may represent a serious obstacle to the longer-term use of these drugs. These late-breaking data in ADOPT, which left no time for comment by the authors [22], are underpinned by findings of reduced bone mineral density (BMD) in older diabetic women [25] and healthy postmenopausal women [26]. The spectre that BMD in diabetic men might also be affected by longer-term treatment with TZDs has also been raised [27].

To emphasize the importance of this action, the US FDA has recently issued warnings in respect of the newly recognized threat of increased limb bone fracture rate associated with both rosiglitazone and pioglitazone [28].

Overall, the results of ADOPT fall short of validating the first-line use of rosiglitazone in T2DM, not least because, as stated in other commentaries, concerns remain regarding both its cost and safety [29,30]. The present data, therefore, are insufficient to justify the displacement of metformin from its position as first-choice treatment of overweight/obese T2DM patients.

Expert commentary

Although ADOPT has demonstrated superior antihyperglycemic durability of rosiglitazone monotherapy when compared with metformin or glibenclamide, the identification of an increased risk of bone fracture in women treated with rosiglitazone has raised further doubts about its long-term safety. Overall, in light of the modest glycemic benefit of rosiglitazone compared with metformin, their cost difference and the additional safety concerns with rosiglitazone, we believe that metformin should remain the rational first choice for overweight/obese patients with T2DM, if monotherapy is considered to be the most appropriate initial therapeutic option.

Future perspective

Often, long-term clinical trials, designed to address a narrow hypothesis in a large patient population, have a habit of finding support for the hypothesis but also of unearthing unexpected and unwanted side-effects. ADOPT, it seems, is no exception to this law of unintended consequences.

Regarding the durability of glycemic control, ADOPT proves the point that a TZD (rosiglitazone in this case) is superior to metformin or glibenclamide, though not markedly so relative to metformin when HbA1c is used as the index rather than FPG. For certain, rosiglitazone does not arrest the progression of T2DM entirely.

Their qualitatively similar effects on peripheral insulin resistance and β-cell function, together with other well-known complementary effects on plasma lipids, the fibrinolytic system and indices of systemic inflammation, might suggest that rosiglitazone and metformin make a potentially handsome duet, with the potential of an optimal two-pronged oral attack to establish early control of T2DM (HbA1c < 6.5%), with some prospect of sustained durability for at least 4–5 years.

However, there may yet be a darker side to this scenario. Until recently, physicians thought they understood the side-effect profile of TZDs fairly well: weight gain, fluid retention, peripheral edema and occasional cases of macular edema and CHF, usually in patients with longstanding T2DM and insulin or sulphonylurea use, renal impairment and prior evidence of significant cardiovascular disease [31–33]. Recent pilot data has also yielded tentative guidance as to how overt fluid retention might be managed [34]. However, the unmasking of an effect of rosiglitazone on fracture risk, which we now know also applies to pioglitazone, is new territory and begs many questions requiring definitive answers.

Unfortunately, whilst this manuscript was in peer review, yet another potential 'issue' with rosiglitazone emerged into the limelight – that of its potential to increase the incidence of acute myocardial infarction [35]. As we make minor revisions here, there is currently a 'tennis match' of claim and counter-claim, involving GlaxoSmithKline (the manufacturer of rosiglitazone), cardiologists at the Cleveland Clinic, editors at the *New England Journal of Medicine*, and US Congressional Democrats and Republicans, with the FDA at the epicentre of what has become an unseemly media circus. Whilst the FDA has responded initially to events by mandating a 'black box' warning for both rosiglitazone and pioglitazone, which relates to their liability to cause CHF, it is both too early and inappropriate for the present authors to speculate on the significance of the myocardial infarction 'signal' or the eventual regulatory outcome for rosiglitazone.

Executive summary

Background

- Progressive deterioration in glycemic control is a pathophysiological signature of Type 2 diabetes mellitus (T2DM), which results in the requirement, in the longer term, for multiple therapies.
- Rosiglitazone belongs to the thiazolidinedione (TZD) class of insulin-sensitizing drugs that act via the nuclear transcription factor, PPAR-γ.

Methods

- A Diabetes Outcome Progression Trial (ADOPT) investigated the durability of antihyperglycemic effects of rosiglitazone, metformin and glibenclamide in 4360 drug-naive patients with T2DM.
- The treatment goal in the trial was an FPG < 140 mg/dl (7.8 mmol/l) and the primary end point was the time from randomization to treatment failure (FPG >180 mg/dl [10 mmol/l]).

Results

- The primary results of ADOPT showed a lower failure rate at 5 years of 15% with rosiglitazone versus 21% with metformin and 34% with glibenclamide, equating to a highly significant risk reduction for rosiglitazone compared with metformin (32%), or glibenclamide (63%).
- Of concern with rosiglitazone was the greater weight gain and an increase in the incidence of fractures in the upper and lower limbs of women.

Significance

- Relative to metformin or glibenclamide monotherapy, rosiglitazone monotherapy changes the course of deteriorating glycemic control in T2DM, at least during the early years after diagnosis.
- Nonetheless, in view of a modest glycemic benefit of rosiglitazone compared with metformin, the cost difference between these treatments and safety concerns with rosiglitazone, metformin remains the rational first choice of agent when initiating drug therapy in overweight or obese patients with T2DM.

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