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Cardiovascular risk of rosiglitazone: another perspective

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Abstract

Rosiglitazone is an effective therapy for type 2 diabetes although concerns have grown about the incidence of oedema and cardiovascular adverse events in patients treated with the drug. The following review was conducted to evaluate further and complement the evidence linking rosiglitazone with an increased risk for cardiovascular adverse events by examining trials and case reports not included in recent meta-analyses. Rosiglitazone-related publications describing case reports and prospective and retrospective cohort analyses were identified using MEDLINE and EMBASE, from July 1999 to July 2007. Relevant reports cited in these publications were also obtained. A recently-published meta-analysis and a double-blind, randomized, placebo-controlled trial were also reviewed. This review of 20 case reports and 10 uncontrolled studies supports the need for added vigilance when prescribing rosiglitazone to patients for the treatment of type 2 diabetes who may be at risk for congestive heart failure. Clinical data from numerous case reports and uncontrolled studies suggested that patients receiving rosiglitazone should be monitored for the development of weight gain or oedema. Prudence should be observed in patients with a history or risk factors for congestive heart failure as they may be poor candidates for rosiglitazone therapy.

Introduction

Type 2 diabetes mellitus is considered an epidemic in the United States. In 2005, it represented 95% of the 14.6 million known cases of diabetes, while an estimated 6.2 million additional cases remain undiagnosed (Centers for Disease Control and Prevention 2007). By 2010, the number of people with diabetes is projected to reach 221 million worldwide (Amos et al 1997). While diabetes is responsible for stroke, blindness, kidney failure and lower-extremity amputations, the most common cause of diabetes-related death is heart disease (Haffner et al 1998; Beckman et al 2002; Centers for Disease Control and Prevention 2007). Not surprisingly, the direct and indirect costs associated with diabetes in the United States exceeded $130 billion in 2002 (American Diabetes Association 2003).

To meet the demand for newer and more effective drug treatments for type 2 diabetes the thiazolidinedione family of medications was introduced during the 1990s. These drugs are potent agonists at the peroxisome proliferator-activated receptor-γ (PPAR-γ), located primarily in adipose tissue, skeletal muscle, and the liver. Activation of PPAR-γ regulates the transcription of insulin-responsive genes controlling the production, transport, and utilization of glucose and also plays a role in regulating fatty acid metabolism (American Diabetes Association 2003).

Rosiglitazone, a thiazolidinedione which received marketing approval in the United States in 1999 (Avandia, GlaxoSmithKline, Inc.), is currently indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, either alone or together with a sulfonylurea, metformin, or insulin when diet, exercise, and other agents do not provide adequate glycaemic control (Avandia Prescribing Information 2007). Clinical data on patients with type 2 diabetes have shown that rosiglitazone is an effective therapy, producing significant reductions in glycosylated haemoglobin A_{1c} and fasting plasma glucose (Lebovitz et al 2001; Phillips et al 2001). Rosiglitazone also significantly improved glycaemic control when coadministered with metformin, sulfonylureas, or insulin (Werner & Travaglini 2001). In addition to improved insulin sensitivity, rosiglitazone decreased blood pressure and fibrinolysis, and improved endothelial dysfunction (Parulkar et al 2001), myocardial glucose uptake (Lautamäki et al 2005) and

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dyslipidaemia (Parulkar et al 2001; Lautamäki et al 2006). Other benefits have included reduced serum levels of matrix metalloproteinase-9 and C-reactive protein (Parulkar et al 2001; Haffner et al 2002; Meisner et al 2006) and serum amyloid A (Meisner et al 2006), suggesting potentially beneficial effects on overall cardiovascular risk. Nevertheless, early use of the drug was associated with reports of serious adverse drug reactions including reports of heart failure soon after initiating rosiglitazone therapy (Wooltorton 2002).

Similar to other thiazolidinediones, rosiglitazone, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate heart failure. In 2001, following growing concerns about cardiac failure and other cardiac effects, a recommendation that patients should be observed for signs and symptoms of heart failure and the drug should be discontinued if any deterioration in cardiac status occurs was added to the product labelling (Avandia Prescribing Information).

Since then, several articles have reviewed the efficacy of rosiglitazone for the treatment of type 2 diabetes mellitus in randomized controlled trials, with an emphasis on cardiovascular safety (Wang et al 2003; Scheen 2004; Vasudevan & Balasubramanyam 2004; Irons et al 2006; Tang 2006). The consensus among the authors of one meta-analysis determined thiazolidinediones, including rosiglitazone, were highly beneficial for the treatment of type 2 diabetes in most instances (Chiquette et al 2004); however, they concluded that the results of on-going long-term studies, such as A Diabetes Outcome Progression Trial (ADOPT) (Viberti et al 2002) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trials (Home et al 2005) were necessary to fully assess their cardiovascular risks.

Another meta-analysis determined the risk for developing peripheral oedema while taking rosiglitazone was considerably greater than when taking pioglitazone (Berlie et al 2007), while yet another meta-analysis reported rosiglitazone represented a greater risk for myocardial infarction and death from cardiovascular causes compared with placebo-treated patients (Nissen & Wolski 2007).

Prompted by these reports, the investigators of the RECORD study published an interim report (Home et al 2007); however, no difference in myocardial infarctions or death from cardiovascular causes was detected due to the lack of statistical power (Home et al 2007). Once again, the conclusion reached by those authors, as well as accompanying discussions (Nathan 2007; Psaty & Furberg 2007) suggested that the safety of rosiglitazone for the treatment of type 2 diabetes was uncertain.

In addition to controlled trials, the medical literature contains a wealth of clinical information about rosiglitazone in the form of uncontrolled studies and case reports. As the extensive meta-analyses described above failed to reach a decision on the safety of rosiglitazone, the following review summarizes the remaining available information regarding rosiglitazone and adverse cardiovascular effects. The intent of this review is to provide pharmacists and health care providers with additional information on the signs, symptoms and clinical course of cardiovascular adverse events reported to occur in association with rosiglitazone, which may help guide the use of this potentially useful drug for the treatment of type 2 diabetes. While it is acknowledged that the use of uncontrolled studies and case reports represent a major limitation to this review, the data presented here further supports the high incidence of pulmonary oedema and heart failure in rosiglitazone-treated patients but not myocardial infarction and death.

Materials and Methods

As the results of randomized controlled trials have been evaluated elsewhere (Nissen & Wolski 2007; Richter et al 2007), the current review has been limited to uncontrolled studies and case reports. A literature search was conducted using the MEDLINE and EMBASE electronic databases. The Medical Subject Headings 'rosiglitazone' AND 'oedema' OR 'cardiovascular disease' OR 'cerebrovascular accident' OR 'coronary events' OR 'heart disease' OR 'heart failure' OR 'myocardial infarction' OR 'stroke' were used. To complement the search, the EMBASE database was also searched using the same keywords. Relevant reports cited in articles identified in the initial search were also obtained. A total of 20 case reports and 10 uncontrolled studies were identified through July 2007 and have been included in this analysis. In addition, one meta-analysis and one randomized controlled trial not included in previous reviews (Nissen & Wolski 2007; Richter et al 2007) were identified.

Results

Cardiovascular effects of rosiglitazone: case reports

The 20 case reports describing cardiovascular adverse events following the administration of rosiglitazone to patients with type 2 diabetes are summarized in Table 1. Two representative case reports are presented below:

The first is a 74 year-old man with type 2 diabetes of 40 years duration. Past medical history included coronary artery disease, well-compensated systolic dysfunction (New York Heart Association (NYHA) class II–III), peripheral vascular disease, gout, hypercholesterolaemia and chronic renal insufficiency. His medications at that time consisted of bumetanide, digoxin, gabapentin, simvastatin, metoprolol and glyceryl trinitrate. Despite the use of glibenclamide 10 mg twice daily, his fasting blood glucose was 250–300 mg dL^{-1}, haemoglobin A_{1c} reached 11.5% and he developed polyuria and polydipsia. Rosiglitazone was started at 4 mg/day, increasing to 8 mg/day after one month. Two weeks later, his weight had increased by 5 kg and he developed shortness of breath, bibasilar rales and +S3 gallop. Twelve days later, he was admitted for heart failure and pulmonary oedema and pitting oedema, which failed to respond to oral diuretics. His weight had now increased by 6.8 kg. The patient received intravenous bumetanide 5 mg twice daily, and a sliding scale

Table 1 Summary of rosiglitazone case reports

Author	Age	Gender	Diabetes duration	Rosiglitazone daily dose, duration	Adverse event	Weight gain	Cardiac history	Other comorbidities	Concomitant diabetes medications*, other medications	Treatment/ outcome
(Thomas & Lloyd 2001)	79	M	?	8 mg 6 months	Pulmonary & peripheral oedema	Yes	Atrial fibrillation, CHF	Renal insufficiency, COPD, HTN	Verapamil, warfarin, ipratropium, albuterol (salbutamol)	Discontinued rosiglitazone; bumetanide, metolazone
(Niemeyer & Janney 2002)	77	M	4 years	4 mg 2 weeks	Peripheral oedema	–	–	Trace peripheral oedema	Glibenclamide*, metformin*	Discontinued rosiglitazone
(Niemeyer & Janney 2002)	53	M	20 years	8 mg[a] 5 months	Peripheral oedema	–	Coronary artery disease, myocardial infarction		Glibenclamide*, acarbose*	Discontinued rosiglitazone, furosemide, insulin
(Page et al 2003)	74	M	40 years	8 mg 2 months	SOB, pulmonary & peripheral oedema	11.8 kg	Coronary artery disease, heart failure (NYHA class II–III)	Peripheral vascular disease, gout, hypercholesterolaemia, chronic renal insufficiency	Bumetanide, digoxin, gabapentin, simvastatin, metoprolol, glyceryl trinitrate (prn), aspirin, paracetamol	Discontinued rosiglitazone, i.v./p.o. bumetanide
(Bell 2003)	51	M	7 years	8 mg 26 months[b]	Peripheral oedema	–	–	–	Insulin*, metformin*, glimepiride*	Discontinued rosiglitazone
(Kermani & Garg 2003)	70	M	–	4 mg 4 weeks	Dyspnoea/tachypnoea, pulmonary & peripheral oedema, cardiomegaly	–	–	HTN, chronic renal insufficiency	Losartan, metoprolol, verapamil, digoxin, aspirin, minoxidil, furosemide, simvastatin	Discontinued rosiglitazone, i.v. furosemide, Prior meds replaced with losartan, felodipine
(Kermani & Garg 2003)	78	M	–	8 mg 5 months	Pulmonary & peripheral oedema, dyspnoea/orthopnoea	–	Coronary bypass surgery	Stable metastatic prostate cancer	Ranitidine, aspirin, DES	Discontinued rosiglitazone; i.v./p.o. furosemide
(Kermani & Garg 2003)	68	M	–	8 mg 3 months	Pulmonary & peripheral oedema	–	–	Obesity, HTN, chronic renal insufficiency	Furosemide, lisinopril	i.v./p.o. furosemide[c]
(Kermani & Garg 2003)	66	M	–	4 mg 6 months	Pulmonary & peripheral oedema, cardiomegaly, dyspnoea/orthopnoea	–	Coronary heart disease, nephritic syndrome, chronic renal insufficiency, HTN	–	Clonidine, felodipine, furosemide, gemfibrozil, L-thyroxine, simvastatin, metoprolol	Discontinued rosiglitazone; i.v. furosemide, p.o. metolazone
(Kermani & Garg 2003)	67	M	–	8 mg 8 months	Peripheral oedema, dyspnoea, paroxysmal nocturnal dyspnoea, cardiomegaly	Yes	Coronary heart disease,	HTN, chronic renal insufficiency	Simvastatin, aspirin, isosorbide, metoprolol, furosemide, lisinopril, felodipine, terazosin	Discontinued rosiglitazone; furosemide, metolazone
(Srivastava et al 2004)	64	F	10 years	2 mg 6 months	Pulmonary oedema, CHF	10 kg	Myocardial infarction, coronary artery bypass surgery	HTN, dyslipidaemia, obesity	Insulin*, simvastatin, irbesartan	Discontinued rosiglitazone; i.v./p.o. furosemide
(Srivastava et al 2004)	79	M	18 years	8 mg 18 months	Peripheral oedema, exertional dyspnoea	9 kg	Coronary artery bypass surgery	HTN, dyslipidaemia, obesity	Metformin*, glibenclamide*, atorvastatin, aspirin, furosemide	Discontinued rosiglitazone, increased furosemide

(Continued)

Table 1 *(Continued)*

Author	Age	Gender	Diabetes duration	Rosiglitazone daily dose, duration	Adverse event	Weight gain	Cardiac history	Other comorbidities	Concomitant diabetes medications*, other medications	Treatment/ outcome
(Srivastava et al 2004)	73	M	5 years	8 mg ?	Peripheral oedema	9 kg	Acute myocardial infarction, CHF	Obesity	Metformin*, gliclazide*, verapamil, simvastatin, enalapril, amiloride	Discontinued rosiglitazone, furosemide
(Cheng & Fantus 2004)	50	M	10 years	4 mg 6 weeks	Cardiogenic shock	–	–	Obesity, dyslipidaemia, HTN, prostatectomy	Metformin*, glibenclamide*, lisinopril, metoprolol, atorvastatin	Extensive cardio-pulmonary support
(Singh 2004)	58	M	–	8 mg 8 months	Peripheral oedema, exertional dyspnoea	11 kg	Coronary artery disease, class 1–2 angina	–	Insulin*, metformin*	Discontinued rosiglitazone, furosemide, ibesartan
(Singh 2004)	73	M	–	4 mg 7 months	Pulmonary & peripheral oedema, dyspnoea, paroxysmal nocturnal dyspnoea	9 kg	Coronary artery disease, class 2 angina	HTN	Insulin*	Discontinued rosiglitazone, furosemide
(Wang et al 2004)	54	F	7 years	8 mg 5 months	Pulmonary & peripheral oedema, orthopnoea, exertional dyspnoea, paroxysmal nocturnal dyspnoea	7.2 kg	–	Obesity, dyslipidaemia	Insulin*, metformin*, atorvastatin, calcium, aspirin, benazapril	Decreased rosiglitazone to 4 mg daily, furosemide
(Wang et al 2004)	68	F	7 years	8 mg 10 months	Peripheral oedema, SOB, exertional dyspnoea, cardiomegaly	5.5 kg	–	Dyslipidaemia, hypothyroidism, GERD, depression, paranoid schizophrenia, COPD, osteoarthritis, hysterectomy	Insulin*, metformin*, L-thyroxine, fluoxetine, olanzapine, gemfibrozil, nizatadine, aspirin, paracetamol, ipratropium/ albuterol, celecoxib	None
(Wang et al 2004)	80	M		8 mg 10 months	Peripheral oedema, SOB, exertional dyspnoea	18.6 kg	Coronary artery disease and bypass surgery, myocardial infarction	Obesity, dyslipidae-mia, HTN, peripheral neuropathy, chronic renal insufficiency, deep vein thrombosis, obstructive sleep apnoea, depression, asthma, intermittent oedema	Insulin*, lansoprazole, aspirin, salmeterol, fluticasone, simvastatin, lisinopril, gabapentin, diltiazem, fluoxetine, furosemide (prn), metolazone (prn)	Discontinued rosiglitazone, furosemide, initiated pioglitazone therapy[d], insulin
(Cekmen et al 2006)	73	F	10 years	–	Pulmonary oedema	–	–	HTN, atherosclerotic heart disease	Acarbose*, gliclazide*, isosorbid mononitrate, losartan/hydrochlorothiazide	Discontinued rosiglitazone

[a]Patient previously received troglitazone for two years but was switched to rosiglitazone when troglitazone was withdrawn from the market. [b]Patient previously received troglitazone for 13 months but was switched to rosiglitazone when troglitazone was withdrawn from the market. [c]Rosiglitazone was discontinued when symptoms returned 13 months later. [d]Pioglitazone was discontinued seven months later due to persistent peripheral oedema. CHF, congestive heart failure. COPD, chronic obstructive pulmonary disease. DES, diethylstilbestrol. GERD, gastroesophageal refhux disease. HTN, hypertension. SOB, shortness of breath.

insulin regimen. After two days of diuresis, the patient lost 4.1 kg in weight. On hospital day 5, he was switched to oral bumetanide and discharged to home. Five days later, the patient was readmitted following the return of his symptoms including a weight gain of 11.8 kg. Upon subsequent discharge, rosiglitazone was discontinued and his symptoms did not recur (Page et al 2003; Richter et al 2007).

The second case is a 54 year-old woman with type 2 diabetes mellitus of seven years duration and a history of dyslipidaemia, obesity (101 kg) but no known cardiac disease. Her then current medications included atorvastatin, aspirin, benazapril, insulin and metformin. Her diabetes was poorly controlled by her then current therapy (haemoglobin A_{1c} 8.0%) and rosiglitazone 4 mg daily was started. After four months her haemoglobin A_{1c} decreased to 7.2% although she was observed to gain 2.7 kg in weight. Rosiglitazone was increased to 4 mg twice daily and her insulin dose was reduced. One month later, the patient developed bilateral lower-extremity oedema, orthopnoea, exertional dyspnoea and her weight increase now totalled 7.2 kg. After an additional month, a chest radiograph revealed pulmonary oedema and echocardiography showed tricuspid valve regurgitation and pulmonary hypertension (normal ejection fraction 55–60%). Rosiglitazone was decreased to 4 mg once daily and the patient lost 1.8 kg while receiving oral furosemide for four weeks. The patient's condition slowly improved and after four months the patient showed only trace oedema in her lower extremities and she remained stable on rosiglitazone 4 mg daily with a haemoglobin A_{1c} of 7.4% (Wang et al 2004).

Among the 20 case reports summarized in Table 1, the average patient age was 67.8 years (range 50–80 years) and the average duration of diabetes was 12.6 years (n = 11, range 4–40 years). Most included a history of underlying heart disease (n = 12; 60%), displayed uncontrolled hyperglycaemia despite therapy with other antihyperglycaemic agents (n = 12; 60%), or both (n = 7; 35%). The only cardiovascular adverse event consistently reported in those case reports was peripheral and/or pulmonary oedema. Oedema developed with cumulative doses as low as 54 mg and duration of treatment as short as two weeks; however, it was difficult to determine a definite dose–response relationship for the development of oedema based on those reports. Concomitant medications were inconsistently reported except for metformin, second generation sulfonylureas and insulin. Insulin was concomitantly used with rosiglitazone in only six cases. Previous reviews suggested that only insulin may have potentiated rosiglitazone-induced oedema (Tang & Maroo 2007).

Cardiovascular effects of rosiglitazone: cohort studies

Marceille et al (2004) conducted a retrospective cohort analysis to assess whether rosiglitazone caused or worsened congestive heart failure in patients with insulin-treated type 2 diabetes. For each patient identified (n = 139), hospital medical records were reviewed for the six-month period before and after the initiation of rosiglitazone therapy. Before receiving rosiglitazone, 35 patients (25%) were diagnosed with congestive heart failure compared with 42 patients (30%) following treatment with rosiglitazone; however, only 20 patients (14%) required treatment for signs of congestive heart failure before rosiglitazone compared with 50 patients (36%) after receiving rosiglitazone ($P < 0.0001$). Lower extremity oedema was the most common symptom, occurring in 25 patients (18%) before and 50 patients (36%) after rosiglitazone ($P < 0.0001$) (Marceille et al 2004).

Another study performed a retrospective review of hospital medical records to assess the effectiveness and adverse events associated with thiazolidinediones (n = 203), including rosiglitazone (n = 96) and pioglitazone (n = 107) when used as adjunctive therapy for type 2 diabetes with poor glycaemic control. During the first six months of treatment, rosiglitazone use was associated with improved glycaemic control, but also increased weight gain (mean 2.9 kg, range −5.0–11.5 kg) and a 21% incidence of peripheral oedema, requiring discontinuation of the drug in 4% of patients. In the pioglitazone group, the mean gain was 2.3 kg (range, –5.0–19 kg) and peripheral oedema was observed in 33% of the patients, requiring discontinuation in 7%. None of those drug-related observations were statistically different. Of five patients noted to develop pulmonary oedema, three were treated with rosiglitazone; four had pre-existing congestive heart failure for which they were being treated with diuretics. Thiazolidinedione therapy was discontinued in three of those; however, the specific agents were not indicated (Hussein et al 2004).

In prospective, double-blind trials the incidence of peripheral oedema was 4.8% in the rosiglitazone-treated patients compared with 1.3% in patients receiving placebo. When rosiglitazone was combined with metformin or sulfonylurea, the incidence of oedema increased to 3% and 4%, respectively, compared with 1.1 to 2.2% on metformin or a sulfonylurea alone (Avandia Prescribing Information 2007). Consequently, several retrospective studies assessed the effects of rosiglitazone together with other hypoglycaemic agents. The following retrospective cohort study used a health insurance claims database to compare the incidence of heart failure in type 2 diabetes patients treated with thiazolidinediones and other antihyperglycaemic agents. Patients receiving thiazolidinediones (n = 5441), including pioglitazone (n = 1347), troglitazone (n = 1665), and rosiglitazone (n = 1882), were compared with a cohort of randomly-selected control patients (n = 28 103). Patients diagnosed with heart failure or treated with digoxin or diuretics during the previous year were excluded. After 40 months, 126 thiazolidinedione-treated patients experienced heart failure (2.3%) compared with 397 control patients (1.4%). After controlling for age, prior coronary artery disease, diabetes complications and concomitant medications, thiazolidinedione use was predictive of heart failure (HR 1.7; $P < 0.001$). For specific agents, the hazard ratio (95% CI) was 1.92 (1.24–2.97) for pioglitazone, 1.44 (1.07–1.94) for troglitazone but only statistically significant for rosiglitazone, 2.27 (1.65–3.13; $P < 0.001$). No dose-relationship was observed for any thiazolidinedione (Delea et al 2003).

Another retrospective cohort study assessed the risk of myocardial infarction and coronary revascularization in type 2 diabetic patients treated with rosiglitazone compared with those treated with other antihyperglycaemic agents.

Using a large health insurance database, hospitalizations due to myocardial infarction or coronary revascularization were identified and incidence rates (95% CI) were determined. Patient groups included those receiving rosiglitazone monotherapy (n = 26 931), rosiglitazone plus one additional oral antihyperglycaemic agent (n = 4086), and rosiglitazone in combination with insulin (n = 2346). The hazard risk (95% CI) for myocardial infarction or coronary revascularization was 1.07 (0.85–1.34) for metformin monotherapy and 0.82 (0.67, 1.02) for sulfonylurea monotherapy, which were no different from rosiglitazone monotherapy. Similarly, the hazard risk with rosiglitazone plus insulin therapy was 0.88 (0.59–1.32), which was no different compared with that of other oral antidiabetic agents plus insulin; however, these investigators suggested that the study population consisting of employed, insured individuals may have been biased towards younger, healthier patients (McAfee et al 2007).

The results of another large, retrospective cohort study of Medicare beneficiaries suggested that the risk of death or readmission following a diagnosis of heart failure was lower in patients receiving thiazolidinediones or metformin monotherapy (Masoudi et al 2005). Similar results were also found using time to death following acute myocardial infarction, although the readmission rate for heart failure was slightly higher for thiazolidinediones (Inzucchi et al 2005). In contrast, Hartung et al (2005) found the prevalence of admission for congestive heart failure was 20.5% among patients receiving a thiazolidinedione compared with 13.1% among control patients ($P < 0.001$), resulting in unadjusted and adjusted odds ratios (95% CI) of 1.71 (1.24–2.36) and 1.37 (0.98–1.92), respectively. Among patients receiving insulin monotherapy, the prevalence of admission was 30.6% compared with controls, resulting in unadjusted and adjusted odds ratios of 1.68 (1.27–2.22) and 1.25 (0.92–1.69), respectively. Among patients receiving a thiazolidinedione plus insulin, the prevalence of admission for heart failure was 9.0% compared with 5.2% for controls, resulting in unadjusted and adjusted odds ratios of 1.81 (1.14–2.86) and 1.35 (0.84–2.18), respectively. No association with hospitalization for heart failure was found for patients exposed to other antihyperglycaemic mediations (Hartung et al 2005). Unfortunately, the specific thiazolidinedione agents were not indicated in those studies.

During an early randomized, placebo-controlled trial, the incidence of oedema was noted to be significantly higher among patients receiving rosiglitazone in combination with insulin (13–16%) compared with insulin alone (4.7%), and was associated with congestive heart failure in four patients treated with insulin plus rosiglitazone vs one patient treated with insulin alone (Raskin et al 2001). The following study assessed the occurrence of oedema in patients receiving the combination of a thiazolidinedione and insulin, at a large medical centre. The study included patients who were receiving thiazolidinedione or insulin monotherapy but later changed to thiazolidinedione plus insulin. Patients taking other medications with a potential for causing oedema, or a loop diuretic, or who already displayed oedema were excluded. Of 79 patients meeting inclusion criteria, 71 patients added a thiazolidinedione to insulin monotherapy, while seven added insulin to thiazolidinedione monotherapy. The mean age was 62 years, most were previously diagnosed with hypertension and hyperlipidaemia and 16% had congestive heart failure. After starting combination therapy, six of the 31 patients taking pioglitazone (30%) developed oedema compared with 14 of the 48 patients (70%) taking rosiglitazone. In total, 20 (25.3%) developed oedema with a mean onset of 135 days. There were no new cases of congestive heart failure or exacerbation of existing congestive heart failure, although one patient developed flash pulmonary oedema and died two months after initiating combined therapy (King & Levi 2004).

Another report described the clinical efficacy of rosiglitazone plus insulin in eight severely obese patients with type 2 diabetes and poor glycaemic control. One patient had hypertension, three had mild, chronic, stable renal failure and four had well-controlled cardiac failure. Four patients were on diuretics for cardiac failure and one for hypertension. Three patients discontinued metformin and no other antihyperglycaemic agents were used. Each patient started rosiglitazone at a dose of 2 mg daily which was doubled every two weeks to a maximum of 8 mg after four weeks. As the maximum effective dose of rosiglitazone was achieved, insulin was adjusted as necessary to reach the desired pre-meal glucose level. The five patients previously taking diuretics experienced peripheral oedema, leading to hospitalization for three of them for intravenous diuretics; however, the oedema was well-controlled while rosiglitazone treatment continued. After 24 weeks, the average percentage change in baseline weight, insulin dose and HbA_{1c} were 2.4, –22 and –16%, respectively. The authors concluded that the use of rosiglitazone plus insulin may be considered in some patients but only under 'specialist supervision' (Buch et al 2002).

In summary, these cohort studies indicated that the use of rosiglitazone was associated with an increased incidence of peripheral oedema (Marceille et al 2004); however, pulmonary oedema was reported primarily in patients with pre-existing heart failure (Hussein et al 2004). The occurrence of peripheral oedema was higher among patients receiving rosiglitazone and insulin (King & Levi 2004). Among rosiglitazone-treated patients, a significant hazard risk was reported for developing heart failure (Delea et al 2003) but not myocardial infarction (McAfee et al 2007).

Safety of rosiglitazone: recent studies

A large meta-analysis designed to assess the cardiovascular effects of rosiglitazone when used for the treatment of type 2 diabetes was already being conducted when the results of Nissen & Wolski (2007) were published and included randomized controlled trials of $\geq$24 weeks duration (range 24–208 weeks, median 26 weeks (Richter et al 2007)). The included studies compared rosiglitazone vs placebo, rosiglitazone vs another oral antidiabetic medication, or rosiglitazone combined with another oral antidiabetic agent or insulin vs the identical combination of an oral antidiabetic agents or insulin. The analysis included 18 studies in which 3888 patients were treated with rosiglitazone.

The results of this meta-analysis were unable to provide any evidence to support a clinically beneficial effect of

rosiglitazone on any health-related outcomes, including mortality and morbidity, adverse effects, or quality of life when used for the treatment of diabetes. Using glycosylated haemoglobin A_{1c} as a surrogate marker for efficacy, there were no clinically-relevant differences between rosiglitazone and other oral antidiabetic agents; however, the incidence of oedema was significantly increased with an odds ratio (95% CI) of 2.27 (1.83–2.81) (Richter et al 2007). Interestingly, those authors used the data from Nissen & Wolski (2007) to perform a meta-analysis on myocardial infarction rates from rosiglitazone vs other monotherapy and rosiglitazone vs combination therapies, but were unable to confirm a significant difference between rosiglitazone vs control (Richter et al 2007). Nevertheless, a third meta-analysis of five randomized double-blind clinical trials revealed that the relative risk (95% CI) for developing rosiglitazone-related congestive heart failure was 2.18 (1.44, 3.32; $P = 0.02$), while the relative risk for death was not different from the controls ($P = 0.63$) (Lago et al 2007).

None of the above meta-analyses included the then recently-published results of Dargie et al (2007), who conducted a 52-week, double-blind, randomized, placebo-controlled study to assess the effects of rosiglitazone on cardiac structure and function as determined by echocardiography in 224 patients with poorly controlled type 2 diabetes and pre-existing chronic heart failure. Patients randomly received rosiglitazone (n = 110) or placebo (n = 114) in addition to previous antidiabetic therapy. Treatment was titrated upward to achieve fasting plasma glucose < 126 mg dL^{-1}. The left ventricular ejection fraction was similar in both groups at baseline and after 52 weeks of treatment (< 40%; $P = 0.1$). After 52 weeks of treatment, glycaemic control was significantly better in the rosiglitazone group ($P < 0.0001$) and left ventricular ejection fraction in patients with type 2 diabetes and heart failure was not adversely affected; however, weight gain was substantially greater in rosiglitazone-treated (1.3 ± 4.8 kg) vs placebo-treated patients (–0.3 ± 3.2 kg), there were significantly more episodes of new or worsening oedema in the rosiglitazone group (n = 28, 25.5%) vs placebo (n = 10, 8.8%; $P = 0.005$) and the use of medications for the treatment of heart failure was greater in the rosiglitazone group (n = 36, 32.7%) vs placebo group (n = 20, 17.5%; $P = 0.037$) (Dargie et al 2007).

Discussion

The recent controversy over the safety of rosiglitazone was sparked by the publication of a meta-analysis by Nissen & Wolski (2007), which concluded that rosiglitazone was associated with a substantial risk for myocardial infarction and cardiovascular death. This was especially troubling as concerns of adverse cardiovascular effects were raised soon after the drug was marketed (Wooltorton 2002). After several months of debate, the validity of that meta-analysis came under scrutiny. The authors of a similar meta-analysis identified a significant risk for the development of oedema in rosiglitazone-treated patients, but were otherwise unable to reproduce the results of Nissen & Wolski (2007). A subsequent critique of the Nissen & Wolski study suggested a selection bias with respect to the trials chosen for inclusion in the analysis, concluding that a risk for myocardial infarction and death from cardiovascular disease for diabetic patients taking rosiglitazone remained to be established (Diamond et al 2007).

Since the publication by Nissen & Wolski (2007), the results of two other randomized trials have become available. The first demonstrated that rosiglitazone significantly improved glycaemic control without affecting left ventricular ejection fraction; however, it was associated with greater incidence of peripheral oedema and worsening heart failure (Dargie et al 2007). The second study, specifically designed to assess the cardiovascular safety of rosiglitazone (Home et al 2005), suggested that there may be a greater incidence of heart failure in the rosiglitazone group but that the results were once again inconclusive.

To complement the recently published meta-analyses, the current review of other data including case reports and uncontrolled studies was conducted in an attempt to determine whether added vigilance should be exercised when prescribing rosiglitazone to patients for the treatment of type 2 diabetes. Among the cohort analyses, which specifically examined rosiglitazone, a significant increase in the number of patients with lower extremity oedema (Marceille et al 2004), pulmonary oedema (Hussein et al 2004) and those requiring treatment for heart failure (Delea et al 2003; Marceille et al 2004) were observed. One study found the hazard risk for myocardial infarction in rosiglitazone-treated patients, with or without insulin, to be no different than patients receiving either metformin or sulfonylurea, alone or in combination with insulin (McAfee et al 2007). Other studies presented conflicting results or were of little value because they were unable to specify the cardiovascular effects of specific thiazolidinediones (Hartung et al 2005; Inzucchi et al 2005; Masoudi et al 2005).

Several potential mechanisms for the adverse cardiovascular effects of rosiglitazone have been proposed. Knock-out mice which are unable to express PPAR-γ in the collecting duct of the kidney were resistant to the rosiglitazone-induced increases in body weight and plasma volume expansion (Guan et al 2005; Zhang et al 2005). Thus, rosiglitazone-induced fluid retention may have been due to PPAR-γ-dependent regulation of renal sodium transport and increased vascular permeability in adipose tissue (Sotiropoulos et al 2006).

PPAR-γ is primarily expressed in adipose tissue (Lee et al 2003); however, it is also found to a lesser extend in non-adipose tissue including the heart, where it appears to regulate myocardial metabolism. The effect of increased PPAR-γ on heart function was assessed in transgenic mice expressing increased PPAR-γ1 in heart tissue. Those animals demonstrated increased cardiac expression of fatty acid oxidation genes and increased lipoprotein triglyceride uptake, resulting in dilated cardiomyopathy associated with increased lipid and glycogen stores, and distorted mitochondrial architecture (Son et al 2007). Thus, heart failure may have been the result of one or a combination of effects.

Regardless of the mechanism responsible for the undesirable cardiovascular effects of rosiglitazone, the information presented here has revealed the clinical dilemma faced by

physicians who treat patients with diabetes. First, inadequately treated diabetes is associated with a high incidence of cardiovascular morbidity and mortality (Haffner et al 1998; Beckman et al 2002), resulting in patients with diabetes and co-morbid heart disease. Second, diabetes is often refractory to commonly-used therapies, such as sulfonylureas, metformin, and insulin. In such cases, treating physicians may have no therapeutic alternative except to add a thiazolidinedione such as rosiglitazone, either alone or in combination with existing therapy. Unfortunately, many of these patients are already at high risk for possible adverse cardiovascular events.

Ideally, physicians should be able to minimize the cardiovascular risk associated with rosiglitazone by avoiding its use in high-risk patients, such as those with congestive heart failure. A study of patients hospitalized with a primary diagnosis of heart failure and concomitant diabetes has suggested that this may not be the case. Among 12 505 such patients, 7.2% were discharged with a prescription for a thiazolidinedione during 1998–1999 despite warnings about their use in patients with heart failure. During 2000–2001, thiazolidinedione use had grown to 16.1% (Masoudi et al 2003). It has been suggested that better communication between cardiologists and endocrinologists who may be independently caring for different manifestations of diabetes in the same patient could improve outcomes in this patient population (Tang 2006).

One prospective study assessed the use of rosiglitazone in eight massively obese patients with poor glycaemic control from oral antihyperglycaemic agents and insulin. Seven achieved significant improvements in glycaemia and were able to substantially reduce their insulin dose. They experienced a median weight increase of 3 kg, which was controlled with diuretics. Those authors concluded that the closely supervised use of rosiglitazone may be considered in some patients (Buch et al 2002). In the study by Dargie et al (2007) similar results were reported despite the presence of heart failure. Together, these data do not appear to support the recent requirement that additional warnings regarding an increased risk for myocardial infarction be added to the rosiglitazone prescribing information (Food and Drug Administration 2007).

Rosiglitazone is an effective antihyperglycaemic agent and may be beneficial when administered to patients with type 2 diabetes who are refractory to treatment with other antihyperglycaemic agents. In such cases, patients must be frequently monitored for sudden oedema, weight gain and evidence of developing or worsening heart failure. Limited data suggested diuretics may be useful for controlling oedema.

Conclusions

Despite new clinical data and additional scrutiny of previous studies, the data supporting the cardiovascular safety of rosiglitazone remain inconclusive. Patients with a history of heart failure may be poor candidates for rosiglitazone therapy and must be monitored closely for the development of weight gain or oedema. Limited data suggested reducing the dose of rosiglitazone and/or the addition of diuretics may alleviate the cardiovascular adverse effects of rosiglitazone in patients with diabetes.

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