

# Rosiglitazone

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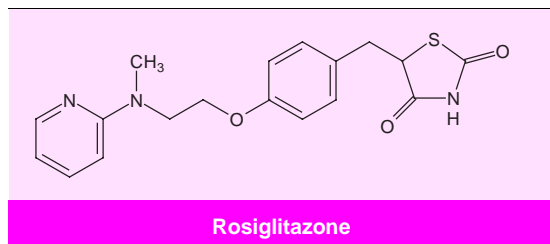
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## Abstract

- ▲ Rosiglitazone, a thiazolidinedione antidiabetic agent, improves insulin resistance, a key underlying metabolic abnormality in most patients with type 2 (non-insulin-dependent) diabetes mellitus.
- ▲ In animal models of insulin resistance, rosiglitazone decreased plasma glucose, insulin and triglyceride levels and also attenuated or prevented diabetic nephropathy and pancreatic islet cell degeneration.
- ▲ In contrast with troglitazone, rosiglitazone does not induce cytochrome P4503A4 metabolism. It does not interact significantly with nifedipine, oral contraceptives, metformin, digoxin, ranitidine or acarbose.
- ▲ In clinical trials in patients with type 2 diabetes mellitus, rosiglitazone 2 to 12 mg/day (as a single daily dose or 2 divided daily doses) improved glycaemic control, as shown by decreases in fasting plasma glucose and glycosylated haemoglobin (HbA<sub>1c</sub>).
- ▲ Addition of rosiglitazone 2 to 8 mg/day to existing sulphonylurea, metformin or insulin therapy achieved further reductions in fasting plasma glucose and HbA<sub>1c</sub>. Oral combinations improved insulin sensitivity and  $\beta$ -cell function according to a homeostasis model assessment.
- ▲ Consistent with its mechanism of action, rosiglitazone appears to be associated with a low risk of hypoglycaemia (<2% of patients receiving monotherapy). There is no evidence to date that rosiglitazone shares the hepatotoxicity of troglitazone.

Features and properties of rosiglitazone (BRL 49653)	
<b>Indication</b>	
Management of type 2 diabetes mellitus	
<b>Mechanism of action</b>	
Thiazolidinedione antidiabetic agent	Insulin sensitiser; peroxisome proliferator activated receptor- $\gamma$ agonist
<b>Dosage and administration</b>	
Usual dosage in clinical trials	2-8 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
<b>Pharmacokinetics (2mg oral dose; fasted versus fed state)</b>	
Peak plasma concentration	152 versus 121 $\mu\text{g/L}$
Time to peak plasma concentration	1.3 versus 3.5h
Area under the plasma concentration-time curve	860 versus 805 $\mu\text{g/L} \cdot \text{h}$
Elimination half-life	3.64 versus 3.78h
<b>Adverse events</b>	
Most frequent	Upper respiratory tract infection
<b>Drug interactions</b>	
No clinically significant interaction with rosiglitazone	Nifedipine, norethindrone, ethinylestradiol, digoxin, metformin, ranitidine, acarbose



Rosiglitazone is a thiazolidinedione, a relatively new class of antidiabetic agents which enhance sensitivity to insulin in the liver, adipose tissue and muscle, resulting in improved insulin-mediated glucose disposal.<sup>[1]</sup> Insulin resistance is a pivotal underlying metabolic abnormality in most patients with type 2 (non-insulin-dependent) diabetes mellitus. Hypersecretion of insulin occurs until the pancreas can no longer compensate for the reduced sensitivity of the tissues to insulin and then overt type 2 diabetes results (reviewed by Henry<sup>[2]</sup> and Bloomgarden<sup>[3]</sup>).

In all animal and human studies discussed in this article, drugs were given orally unless specified otherwise. In animal studies, dosages are expressed per kg bodyweight unless specified otherwise.

## 1. Pharmacodynamic Profile

### Mechanism of Action

The mechanism of action of rosiglitazone and other members of its class is yet to be clarified. Available data suggest that these agents can modulate several processes to increase sensitivity to insulin. These include effects on insulin receptor kinase activity, insulin receptor phosphorylation, numbers of insulin receptors and hepatic glucose metabolism.<sup>[4]</sup> However, it has been suggested that many of the glucoregulatory effects of thiazolidinediones are mediated via reduced systemic and tissue lipid availability.<sup>[5]</sup>

One key action of thiazolidinediones is to activate the nuclear receptor peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ).<sup>[6-8]</sup> This receptor, which is expressed at high levels in mammalian adipose tissue, regulates the transcription of several genes involved in preadipocyte differentiation

and insulin-mediated glucose uptake in peripheral tissues. Thiazolidinediones promote adipose cell differentiation by activating PPAR- $\gamma$ . They reduce expression of leptin (a signalling factor expressed by the *ob* gene which regulates appetite, body-weight and energy balance) and tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), while increasing expression of lipoprotein lipase, adipocyte lipid-binding protein (aP2) and GLUT-4 (which plays a key role in the facilitated transport of glucose into adipocytes and skeletal muscle).<sup>[8]</sup>

- Rosiglitazone binds to PPAR- $\gamma$  with high affinity [dissociation constant ( $K_d$ ) approximately 40 nmol/L].<sup>[6]</sup> It has a higher affinity for PPAR- $\gamma$  in intact human adipocytes ( $IC_{50}$  10 nmol/L) than pioglitazone (360 nmol/L) or troglitazone (1050 nmol/L).<sup>[9]</sup>

- Exposure of pluripotent C3H10T1/2 stem cells<sup>[6]</sup> or human preadipocytes<sup>[10]</sup> to rosiglitazone at concentrations as low as 100 nmol/L *in vitro* promoted their differentiation to adipocytes.<sup>[6]</sup> PPAR- $\gamma$  expression in C3H10T1/2 cells was increased 3-fold.<sup>[6]</sup>

- Rosiglitazone inhibited leptin gene expression in rat 3T3-L1 adipocytes *in vitro*,<sup>[11,12]</sup> with an  $ED_{50}$  (concentration causing 50% inhibition) of 5 to 50 nmol/L, similar to its  $K_d$  for binding to PPAR- $\gamma$  (40 nmol/L) and identical to its  $ED_{50}$  for inducing adipocyte differentiation (5 to 50 nmol/L).<sup>[12]</sup>

- In *in vivo* studies in obese or high-fat-diet-fed rats, rosiglitazone reduced *ob* mRNA levels in epididymal fat pads (by 40% at 5 mg/kg/day)<sup>[11]</sup> and reduced plasma leptin levels ( $\approx 40\%$ ;  $p < 0.05$ ).<sup>[13,14]</sup> Expression of PPAR- $\gamma$  and aP2 mRNA were significantly increased ( $p < 0.01$ ).<sup>[13]</sup>

- Lipoprotein lipase mRNA and activity in epididymal adipose tissue increased by more than 2-fold after administration of rosiglitazone 5 or 10 mg/kg for 7 days to normal rats. A similar increase in mRNA levels was seen when the drug (10  $\mu$ mol/L) was added to adipocytes *in vitro*.<sup>[15]</sup>

- Rosiglitazone enhanced expression of uncoupling proteins 1<sup>[16,17]</sup> and 3<sup>[17]</sup> (UCP-1 and UCP-3) [by 5- and 3-fold, respectively, at a concentration of 1  $\mu$ mol/L<sup>[17]</sup>] in rat or human adipocytes *in vitro*.

Synergistic effects on UCP-3 were noted between rosiglitazone and the PPAR- $\alpha$  agonist Wy 14643,<sup>[17]</sup> which antagonised the effects of rosiglitazone on UCP-1.<sup>[18]</sup> Rosiglitazone also increased expression of UCP-2 in adipocytes.<sup>[19]</sup>

- Insulin binding to white adipocytes from obese mice was significantly ( $p < 0.001$ ) increased by pretreatment with rosiglitazone (30  $\mu\text{mol/kg}$  of diet for 14 days). The drug appeared to increase the number of insulin receptors rather than change receptor affinity and increased the total tissue content of GLUT-4 by 2.5-fold.<sup>[20]</sup>

#### Effects on Glucose and Lipid Metabolism

- In genetic and dietary animal models of obesity and insulin resistance, including the obese hyperglycaemic *db/db* mouse,<sup>[7,21,22]</sup> *ob/ob* mouse,<sup>[20,21]</sup> Zucker fatty (*fa/fa*) rat<sup>[23-27]</sup> and overfed Wistar rat,<sup>[5,14]</sup> rosiglitazone significantly reduces plasma levels of glucose, insulin and/or triglycerides. Rosiglitazone also lowered plasma levels of non-esterified fatty acids<sup>[5,23,28]</sup> and ketone bodies.<sup>[5]</sup>

- As with other thiazolidinediones,<sup>[8]</sup> the *in vivo* antidiabetic potency of rosiglitazone was correlated with its binding affinity for PPAR- $\gamma$ .<sup>[7]</sup>

- Rosiglitazone had a greater effect on plasma triglycerides than on plasma glucose in Zucker fatty rats, improving dyslipidaemia at a dosage (10 to 30 mg/kg/day) which did not significantly lower plasma glucose levels.<sup>[27]</sup> In normal rats, rosiglitazone decreased serum triglycerides without affecting plasma glucose levels.<sup>[15]</sup>

- As with other thiazolidinediones,<sup>[8]</sup> rosiglitazone frequently increases food intake and promotes bodyweight gain and/or fat deposition in rodents.<sup>[11,14,15,25,29]</sup> However, no significant effect of thiazolidinediones on body fat mass has been reported in humans to date.<sup>[16]</sup> Specifically, thiazolidinediones increase the amount of brown adipose tissue (which dissipates energy via oxidation of fatty acids),<sup>[8]</sup> which might contribute to the effects of these drugs on insulin resistance.<sup>[16]</sup> Rosiglitazone enhanced rat interscapular brown adipose tissue mass.<sup>[30]</sup>

- Glucose tolerance in *ob/ob* mice was improved by rosiglitazone; at 100  $\mu\text{mol/kg}$  of diet, the rise in blood glucose levels following an oral glucose load was completely abolished.<sup>[20]</sup> When given to young Zucker fatty rats (aged 6 weeks), rosiglitazone ( $\approx 10 \mu\text{mol/kg}$ ) prevented development of hyperglycaemia, maintaining blood glucose levels similar to those in lean rats.<sup>[31]</sup>

- Under euglycaemic clamp conditions, rosiglitazone (10  $\mu\text{mol/kg/day}$  for 4 days) increased glucose uptake, insulin suppressibility of hepatic glucose production and muscle glucose uptake; however, these effects were seen only in insulin-resistant rats.<sup>[5]</sup>

- Prior administration of rosiglitazone 3 mg/kg/day for 7 days to obese Zucker rats restored basal glucose uptake in the isolated perfused heart (from 42 to 15% lower than in lean control hearts).<sup>[23]</sup>

- Prior administration of rosiglitazone 3  $\mu\text{mol/kg/day}$  to obese Zucker rats decreased the insulin resistance of perfused hindlimbs, as shown by increased responsiveness to insulin. However, no further details of results were provided.<sup>[32]</sup>

#### Effects on Diabetic Complications

- Administration of rosiglitazone (50  $\mu\text{mol/kg}$  of diet) to Zucker rats protected against development and progression of renal injury and adaptive changes to pancreatic islet morphology which result from sustained hyperinsulinaemia. When given as a preventative strategy to young rats (aged 6 to 7 weeks) for 9 months, rosiglitazone delayed the onset (from 3 to 6 months), and markedly reduced subsequent progression, of proteinuria compared with untreated rats. Delayed progression of proteinuria was also noted when rosiglitazone was administered to older rats (age 24 to 25 weeks) with established proteinuria (intervention group). Normalisation of urinary *N*-acetyl- $\beta$ -D-glucosaminidase activity (a marker for renal proximal tubular damage) and attenuation of the rise in systolic blood pressure that accompanied the development of proteinuria was noted in both groups of rats. Postmortem, histological and ultrastructural examination confirmed the renal protective effect of the drug:

nephromegaly and signs of chronic nephropathy seen in control animals were attenuated or prevented in the prevention group and attenuated in the intervention group. Similarly, pancreatic islet hyperplasia and other pancreatic abnormalities were prevented or attenuated.<sup>[25]</sup>

- Rosiglitazone (30  $\mu\text{mol/kg}$  of diet for 10 days) significantly increased the area, number and insulin content of pancreatic islets in *db/db* mice, possibly reflecting reduced secretory pressure on the  $\beta$ -cell after normalisation of hyperglycaemia. Insulin and amylin gene expression were unchanged in this model.<sup>[22]</sup> However, in another study hyperexpression of these genes in Zucker fatty rats was reduced ( $\approx 50\%$ ) by rosiglitazone administration (3  $\mu\text{mol/kg/day}$  for 21 days).<sup>[33]</sup>

- Rosiglitazone (50  $\mu\text{mol/kg}$  of diet) protected against impaired endothelial function when given to young Zucker rats for 9 to 12 weeks. Vasorelaxant responses of isolated mesenteric resistance vessels to insulin and acetylcholine were partially preserved.<sup>[24]</sup>

## 2. Pharmacokinetics and Drug Interactions

- Administration of rosiglitazone with food reduced the rate, but not the extent, of absorption of the drug. A crossover study in 12 healthy volunteers found that area under the concentration-time curve extrapolated to infinity ( $\text{AUC}_{0-\infty}$ ) after administration of rosiglitazone 2mg was similar in the fasted and fed state (860 versus 805  $\mu\text{g/L} \cdot \text{h}$ ), but mean maximum plasma concentration ( $C_{\text{max}}$ ) was reduced by 20% (from 152 to 121  $\mu\text{g/L}$ ) and time to  $C_{\text{max}}$  ( $t_{\text{max}}$ ) was delayed by 2.2 hours (1.3 vs 3.5 hours), by food intake. Elimination half-life ( $t_{1/2\beta}$ ) was 3.64 versus 3.78 hours.<sup>[34]</sup>

- Comparison of pharmacokinetics in young (aged 18 to 45 years) and elderly (aged  $\geq 65$  years) healthy volunteers after a single 4mg dose of rosiglitazone showed that  $\text{AUC}_{0-\infty}$  and  $C_{\text{max}}$  were 36 and 38% lower in the older group. However,  $t_{1/2}$  and  $t_{\text{max}}$  were similar in the 2 age groups.<sup>[35]</sup>

- The pharmacokinetics of rosiglitazone were unaltered by mild to moderate renal impairment<sup>[36]</sup> or end-stage renal failure with haemodialysis.<sup>[37]</sup> The unbound drug fraction was almost 40% higher in patients with severe renal impairment;<sup>[36]</sup> nevertheless, adjustment of rosiglitazone dosage is not necessary on the basis of impaired renal function.<sup>[36,37]</sup>

- However, dosage reduction is required in patients with impaired hepatic function: total and unbound AUC were increased by approximately one-third and 3-fold, respectively and  $t_{1/2\beta}$  by approximately 1.5-fold (6.0 vs 3.8 hours) compared with healthy volunteers.<sup>[38]</sup>

- In contrast with troglitazone,<sup>[39]</sup> rosiglitazone does not appear to induce cytochrome P450 (CYP) 3A4 metabolism. Concomitant administration of rosiglitazone (8 mg/day for 14 days) did not affect the pharmacokinetics of the CYP3A4 substrates nifedipine<sup>[40]</sup> or ethinylestradiol or norethindrone (in a combined oral contraceptive formulation).<sup>[41]</sup>

- Similarly, rosiglitazone did not interact with ranitidine,<sup>[42]</sup> metformin<sup>[43]</sup> or digoxin.<sup>[44]</sup>

- Administration of acarbose (100mg 3 times daily for 7 days) slightly reduced absorption (AUC; 12%) of a single 8mg dose of rosiglitazone and prolonged  $t_{1/2}$  by approximately 1 hour. However, this was not considered clinically relevant.<sup>[45]</sup>

## 3. Therapeutic Trials

Rosiglitazone has been evaluated in clinical trials in patients with type 2 diabetes. Generally, patients had previously been managed with diet or other antidiabetic agents and treatment with rosiglitazone was preceded by a placebo or no-treatment run-in period of 3 to 8 weeks. Mean baseline fasting plasma glucose (FPG) and glycosylated haemoglobin ( $\text{HbA}_{1c}$ ) were  $>10.2 \text{ mmol/L}$  and  $>8\%$ , respectively, in all studies. Changes in  $\text{HbA}_{1c}$  are expressed as absolute reductions or increases from baseline or placebo.

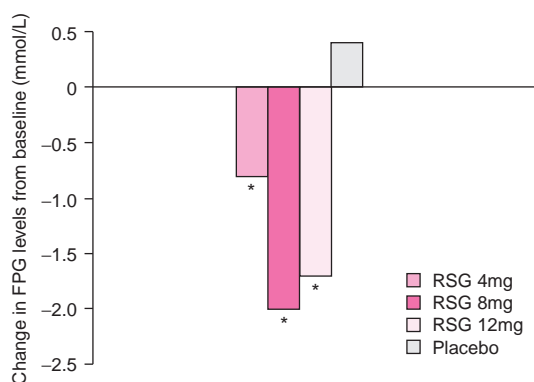
### Dose-Ranging Studies

- A 12-week double-blind multicentre study compared rosiglitazone 0.05, 0.25, 1 or 2mg twice daily

with placebo in 380 patients. The 1 and 2mg twice daily dosages were effective in reducing FPG; ( $p = 0.001$ ) and fructosamine ( $p = 0.003$  for 2mg twice daily group) from baseline, but HbA<sub>1c</sub> was not significantly reduced in any of the treatment groups. The higher dosage also reduced plasma insulin (by 2.7 mIU/L;  $p = 0.0044$ ) and free fatty acid ( $p = 0.0014$ ) levels and increased total, high density lipoprotein (HDL)- and low density lipoprotein (LDL)-cholesterol ( $p < 0.001$ ).<sup>[46]</sup>

- Once daily treatment with rosiglitazone 4, 8 or 12 mg/day for 8 weeks significantly reduced FPG, by 0.8, 2.0 and 1.7 mmol/L (15.8, 35.7 and 30.2 mg/dl), respectively ( $p < 0.0001$  for all doses). FPG increased by 0.4 mmol/L (7.4 mg/dl) in placebo recipients in this randomised double-blind study in 369 patients. 8 mg/day was more effective than 4 mg/day, but no additional antihyperglycaemic effect was seen with 12 mg/day (fig. 1). Over 50% of patients treated with the 2 highest dosages had an FPG reduction of  $>1.7$  mmol/L ( $>30$  mg/dl).<sup>[47]</sup>

- A randomised placebo-controlled study compared rosiglitazone 4 and 8 mg/day, given as a single daily dose or in 2 divided daily doses, in 959 patients (treatment duration not stated). HbA<sub>1c</sub> and FPG decreased significantly without any increase



**Fig. 1.** Antihyperglycaemic efficacy of once daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels after receiving RSG 4, 8 or 12mg once daily or placebo for 8 weeks in a randomised double-blind study in 369 patients with type 2 diabetes mellitus.<sup>[47]</sup>  
\*  $p < 0.0001$ .

in serum insulin levels in all active treatment groups. Compared with placebo, HbA<sub>1c</sub> decreased by 0.8, 0.9, 1.1 and 1.5% in the rosiglitazone 4mg once daily, 2mg twice daily, 8mg once daily and 4 mg twice daily treatment groups ( $p < 0.0001$  all comparisons).<sup>[48]</sup>

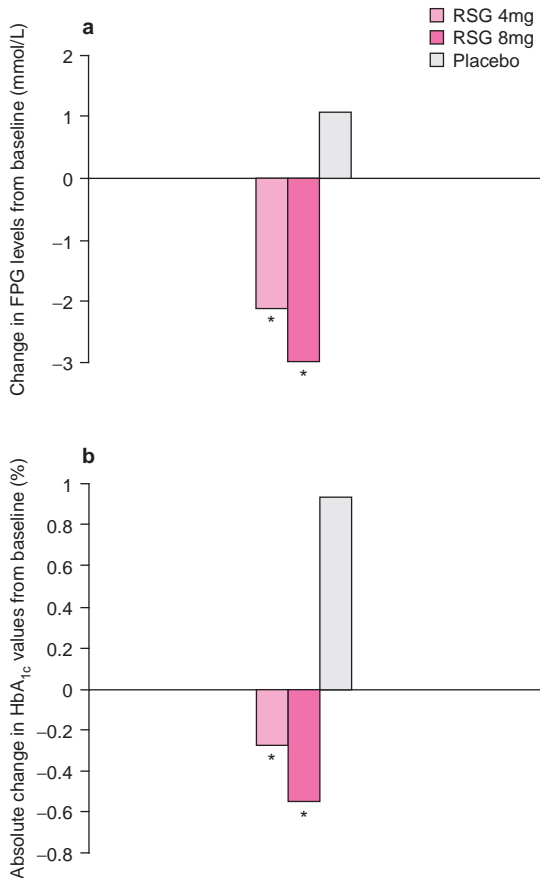
- In a multicentre, placebo-controlled 26-week study in 493 patients, rosiglitazone 2 or 4mg twice daily reduced FPG and HbA<sub>1c</sub> by 2.1 and 3 mmol/L (38.4 and 54.0 mg/dl) and 0.28 and 0.56%, respectively, from baseline ( $p < 0.0001$  vs placebo). These parameters increased by 1.0 mmol/L (18.9 mg/dl) and 0.92% in placebo recipients (fig. 2). Serum fructosamine was also significantly reduced by both dosages of rosiglitazone ( $p < 0.0001$  vs placebo).<sup>[49]</sup>

- In a study in 99 patients, treatment with rosiglitazone 2, 4 or 6mg twice daily for 8 weeks significantly decreased the postprandial plasma glucose AUC (by 144.4, 177.1 and 175.0 mg/dl · h, respectively) and plasma insulin AUC (by 34.0, 77.8 and 139.9 pmol/L · h, respectively) [ $p < 0.0004$  vs baseline and placebo for all treatment groups].<sup>[50]</sup>

- Rosiglitazone appeared to be equally effective in older (aged  $\geq 65$  years) and younger ( $< 65$  years) patients. In two 26-week placebo-controlled studies, rosiglitazone 4 and 8 mg/day achieved similar reductions in FPG and HbA<sub>1c</sub> in the 2 age groups.<sup>[51]</sup>

#### Comparison with Glibenclamide

- Rosiglitazone 4mg twice daily was more effective ( $p = 0.033$ ), and rosiglitazone 2mg twice daily was slightly less effective, than optimally titrated glibenclamide (glyburide) in producing sustained reductions in FPG over a 12-month period. 587 patients participated in this randomised, double-blind study. FPG was reduced by 1.4, 2.3 and 1.7 mmol/L (25, 41 and 30 mg/dl) with rosiglitazone 4 mg/day, rosiglitazone 8 mg/day and glibenclamide, respectively, and 36, 51 and 37% of patients had levels  $< 7.8$  mmol/L (140 mg/dl) after treatment. Rosiglitazone 8 mg/day was slightly, but not significantly, less effective than glibenclamide in reducing HbA<sub>1c</sub> (by 0.53 vs 0.72%).<sup>[52]</sup>



**Fig. 2.** Antihyperglycaemic efficacy of twice daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels (a) and glycosylated haemoglobin (HbA<sub>1c</sub>) (b) after receiving RSG 2 or 4mg twice daily or placebo in a multicentre 26-week study in 493 patients with type 2 diabetes mellitus.<sup>[49]</sup> \*  $p < 0.0001$ .

### Use in Combination with Other Agents

Studies evaluating rosiglitazone as combination treatment with sulphonylureas, metformin or insulin were all randomised and placebo-controlled.

- Addition of rosiglitazone 2 or 4 mg/day (in 2 divided daily doses) to existing sulphonylurea therapy (gliclazide, glibenclamide, glipizide) for 6 months produced additional reductions in HbA<sub>1c</sub> (0.6 and 1.0%;  $p < 0.0001$ ) and FPG (1.3 and 2.4 mmol/L; 24.3 and 43.9 mg/dl). Worsening of these parameters occurred in placebo recipients. 574 pa-

tients participated in this double-blind study. Over half of patients treated with the higher dosage of rosiglitazone achieved a reduction of  $\geq 0.7\%$  in HbA<sub>1c</sub> and  $\geq 1.7$  mmol/L (30 mg/dl) in FPG. Free fatty acids decreased by approximately 15% and HDL- and LDL-cholesterol increased by 10 and 5%, respectively, in this treatment group.<sup>[53]</sup>

- In patients ( $n = 348$ ) poorly controlled by maximal metformin therapy (2.5 g/day), addition of rosiglitazone 4 or 8 mg/day (once daily) for 26 weeks improved glycaemic control without changing serum insulin levels. FPG decreased by 2.2 and 2.9 mmol/L (39.8 and 52.9 mg/dl) and HbA<sub>1c</sub> by 0.97 and 1.18%, respectively ( $p < 0.0001$  all comparisons). FPG levels  $< 7.8$  mmol/L (140 mg/dl) were achieved in 22 and 30% of patients, respectively, despite mean baseline levels of  $> 11.7$  mmol/L (210 mg/dl).<sup>[54]</sup>

- In patients ( $n = 319$ ) poorly controlled on twice daily insulin, addition of rosiglitazone 2 or 4mg twice daily significantly improved glycaemic control and lowered insulin requirements (by 4.8 and 9.4 U/day, respectively;  $p < 0.006$  both comparisons) [fig. 3]. Over the 26-week study period, FPG was reduced by 2.3 and 2.5 mmol/L (41.5 and 44.4 mg/dl) from baseline with rosiglitazone 4 and 8 mg/day, respectively, but increased by 0.6 mmol/L (10.3 mg/dl) in placebo recipients. HbA<sub>1c</sub> was decreased by 0.6 and 1.2% compared with an increase of 0.1% in the placebo group. Over half of patients receiving the higher dose of rosiglitazone had a decrease of  $\geq 1\%$  in HbA<sub>1c</sub>.<sup>[55]</sup>

### Homeostasis Model Assessment

- Treatment with rosiglitazone 2 to 8 mg/day with or without sulphonylureas or metformin for 26 weeks decreased insulin resistance ( $\approx 3$  to 25%) and improved  $\beta$ -cell function ( $\leq 94\%$ ), according to a homeostasis model assessment (HOMA).<sup>[56]</sup> Insulin resistance increased in those who received placebo or sulphonylurea monotherapy and did not improve in those treated with metformin (fig. 4).<sup>[57,58]</sup>

#### 4. Tolerability

- Analysis of pooled data from 4327 patients treated with rosiglitazone, alone or in combination with metformin or sulphonylureas, showed that the only adverse events reported in  $\geq 5\%$  of patients receiving rosiglitazone were upper respiratory tract infection (13.1% of monotherapy recipients), injury (8.9%) and headache (6.7%). The relationship of these events to treatment was not stated. Adverse events related to the cardiovascular system, elevated serum lipids, anaemia or oedema were at least as common with placebo as with rosiglitazone.<sup>[59]</sup> Overall, fewer rosiglitazone than placebo recipients withdrew from clinical trials because of adverse events ( $\leq 6.2$  to  $7.8\%$  vs  $10.8\%$ ).<sup>[48,59]</sup>

- According to an analysis of 2526 rosiglitazone-treated patients, the proportions of patients with at least 1 adverse event did not differ between elderly (aged  $\geq 65$  years) and younger patients. As with younger patients, the most common events in the elderly were upper respiratory tract infection, injury and headache and these were equally common in the 2 age groups. However, oedema and anaemia appeared to be more common in the elderly ( $7.5$  vs  $3.5\%$  and  $2.5$  vs  $1.7\%$ ).<sup>[51]</sup>

- Coadministration of rosiglitazone did not increase the frequency of hypoglycaemia associated with sulphonylureas or increased plasma lactate

levels or gastrointestinal events associated with metformin.<sup>[59]</sup>

#### Hypoglycaemia

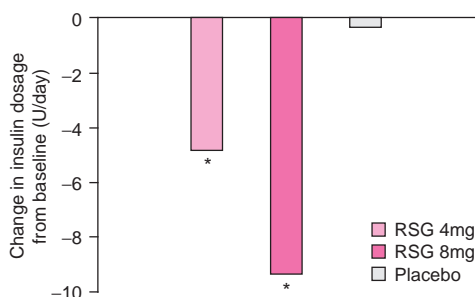
- Hypoglycaemia occurred in  $<1\%$  of 2526 patients receiving rosiglitazone (dosage not stated) in clinical trials.<sup>[51]</sup> In a comparative study, hypoglycaemia was more common with glibenclamide (optimally titrated;  $12\%$  of 203 patients) than with rosiglitazone 4 or 8 mg/day ( $<2\%$  of 384 patients).<sup>[52]</sup>

- Rosiglitazone did not appear to increase the risk of hypoglycaemia associated with moderate alcohol intake ( $0.6$  g/kg) with a meal. Concomitant intake of alcohol did not produce any clinically meaningful changes in plasma glucose or overnight urinary cortisol : creatinine ratios in patients who received rosiglitazone 8 mg/day ( $n = 11$ ) or placebo ( $n = 12$ ) for 8 weeks. Hypoglycaemia did not occur.<sup>[60]</sup>

#### Effects on the Liver

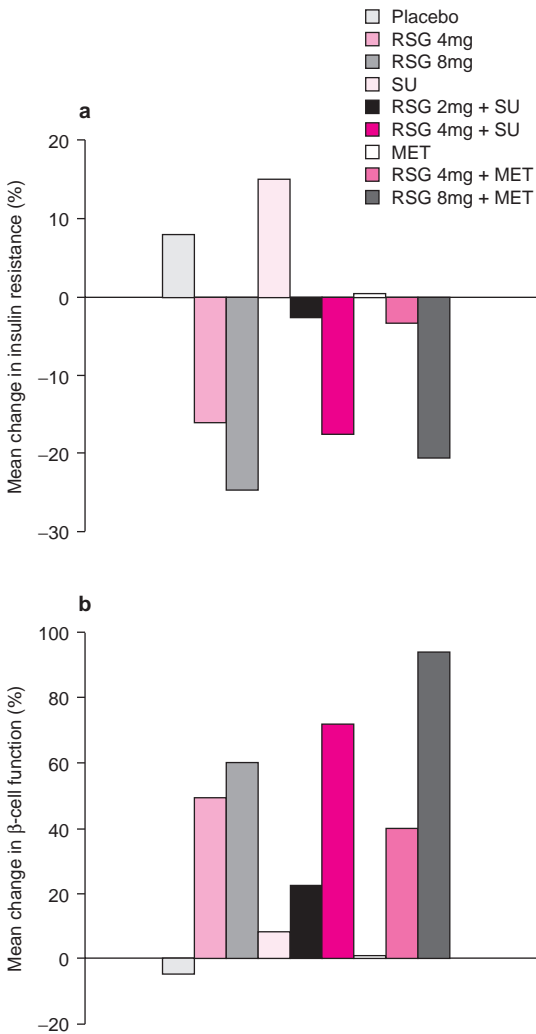
Troglitazone has been found to cause significant hepatic toxicity, which has resulted in death or the need for liver transplantation in a small number of patients.<sup>[39]</sup> Thus, concern has been raised as to whether this is a class effect of thiazolidinediones. To date, there is no evidence that rosiglitazone is hepatotoxic.

- Pooled data are available from  $>4500$  patients treated with rosiglitazone for  $\geq 6$  months in double-blind or open-label studies. Of 3455 patients who had frequent liver function tests (every 4 weeks for the first 3 months, every 6 weeks for the next 3 months and quarterly thereafter) in double-blind controlled studies, the proportion of patients with serum ALT levels  $>3$  times the upper limit of normal ( $>3 \times \text{ULN}$ ;  $0.17\%$ ;  $n = 6$ ) was similar to that in patients receiving placebo ( $0.18\%$ ;  $n = 1$  of 561) or sulphonylureas or metformin ( $0.48\%$ ;  $4/828$ ). [Patients with baseline ALT or AST values  $\leq 2.5 \times \text{ULN}$  were allowed to enter the studies.] Of 13 patients who developed ALT levels  $>3 \times \text{ULN}$  during rosiglitazone treatment (during controlled clinical



**Fig. 3.** Efficacy of rosiglitazone (RSG) in combination with insulin. Effects on insulin requirements of adding RSG 2 or 4mg twice daily or placebo to existing twice daily insulin therapy in patients ( $n = 319$ ) with poorly controlled type 2 diabetes mellitus who participated in a randomised study.<sup>[55]</sup> \*  $p < 0.006$ .





**Fig. 4.** Effects of rosiglitazone (RSG) and other antidiabetic agents on insulin resistance (a) and  $\beta$ -cell function (b) in a homeostasis model assessment. Patients participating in 3 clinical trials received placebo (n = 158), RSG 2mg twice daily (n = 166), RSG 4mg twice daily (n = 169), sulphonylurea therapy (SU; n = 192), RSG 1mg twice daily + SU (n = 199), RSG 2mg twice daily + SU (n = 183), metformin (MET; n = 113), RSG 4mg once daily + MET (n = 116), RSG 8mg once daily + MET (n = 110) for 26 weeks.<sup>[57,58]</sup>

trials or open-label treatment), levels either improved, normalised or did not worsen during continued therapy (follow-up data were not available for 2 patients).<sup>[61]</sup>

• These data are supported by the results of a study in rat hepatocytes. In contrast to troglitazone, which was toxic to these cells at a concentration of 20  $\mu\text{mol/L}$ , rosiglitazone showed no cytotoxicity at concentrations  $\leq 100 \mu\text{mol/L}$ .<sup>[62]</sup>

Effects on the Cardiovascular System

• As with other thiazolidinediones, rosiglitazone has been associated with small and/or clinically insignificant decreases in haematocrit and haemoglobin in patients with type 2 diabetes.<sup>[46,49]</sup> Rosiglitazone 4 or 8 mg/day for 8 weeks did not affect indices of erythropoiesis or red blood cell destruction in healthy volunteers (n = 30). Haemoglobin and haematocrit were reduced slightly (0.6 g/L and 2%, respectively) in the 8mg dosage group, presumably as a result of increased plasma volume.<sup>[63]</sup>

• Cardiac hypertrophy has been noted in rodents given high doses of thiazolidinediones. However, treatment of 104 patients with rosiglitazone 4mg twice daily for up to 52 weeks did not result in any adverse changes in cardiac structure or function, on the basis of echocardiographic studies. Only small and clinically unimportant changes were seen in left ventricular mass index and left ventricular end diastolic volume. Ejection fraction was unchanged. Similar results were seen in patients treated with glibenclamide (mean 10.5 mg/day) over the same time period. Diastolic blood pressure was lowered by 2.3mm Hg (p = 0.0016) in rosiglitazone recipients, as assessed by 24-hour ambulatory monitoring.<sup>[64]</sup>

• Similarly, no changes in left ventricular mass were detected on echocardiography in 380 patients treated with rosiglitazone 0.1 to 4 mg/day or placebo for up to 12 weeks.<sup>[65]</sup>

• Thiazolidinediones can cause oedema and haemodilution, and animal studies have shown that troglitazone has a vasodilatory effect which might lead to fluid retention. However, an *in vitro* study in human resistance vessels showed that rosiglitazone did not have the direct vasorelaxant effect noted with troglitazone. Troglitazone also had a similar vasodilatory effect in Wistar rat arteries that was not abolished by  $\text{N}^G$ -nitro-L-arginine methyl ester.



Further studies are required to determine whether these differences are apparent *in vivo*.<sup>[66]</sup>

## 5. Rosiglitazone: Current Status

Rosiglitazone is a thiazolidinedione insulin sensitiser that has been filed for approval for the management of type 2 diabetes mellitus.

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