



Fixed-dose combination rosiglitazone/glimepiride in the treatment of Type 2 diabetes mellitus

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Rosiglitazone and glimepiride are effective antihyperglycemic agents approved for the treatment of Type 2 diabetes mellitus. Primarily, rosiglitazone increases insulin sensitivity, while glimepiride stimulates insulin release from β -cells in the pancreas. Combination therapy is often required to achieve effective glycemic control. A fixed-dose formulation of rosiglitazone plus glimepiride has recently been approved in the EU and US for treatment of Type 2 diabetes. Much data demonstrate the advantages of the combination therapy compared with rosiglitazone or glimepiride as monotherapy. Rosiglitazone plus glimepiride is generally well tolerated in all studies and presents a tolerability profile similar to that of monotherapy with rosiglitazone and sulphonylurea. The aim of this review is to present this new fixed-dose combination, which represents a promising new strategy to obtain recommended glycemic control.

Type 2 diabetes mellitus is a complex metabolic disorder characterized by a variable degree of insulin resistance, impaired insulin secretion and excessive hepatic glucose production; all these factors contribute to hyperglycemia. The decreased ability of insulin to act effectively on peripheral tissues results from a combination of genetic susceptibility and environmental factors, the most important being obesity, particularly visceral or central. Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose release, which predominantly accounts for increased fasting plasma glucose (FPG) levels, while the decrement of peripheral glucose utilization is principally related to postprandial hyperglycemia. In skeletal muscle, impairment in glycogen formation (nonoxidative metabolism) is greater than in glycolysis (oxidative metabolism). In Type 2 diabetes, the mechanisms that underlie insulin resistance are not understood completely. Postreceptor defects are believed to play the most important role in insulin resistance. The pathogenesis of insulin resistance is currently focused on phosphatidylinositol (PI)3-kinase signaling defects, which determine a large number of abnormalities, such as a reduced translocation of glucose transporter (GLUT)4 to the plasma membrane. In the earlier stages of Type 2 diabetes mellitus, insulin secretion increases in response to insulin resistance so that, initially, secretory defects are minimal and related selectively to glucose-stimulating insulin secretion and the

response to other secretagogues is preserved. During the natural history of the disorder, a progressive decline of insulin secretion is the rule and leads to a state of large inadequate insulin secretion. The metabolic disorders in diabetes negatively affect pancreatic islet function. Chronic hyperglycemia determines an impairment in β -cell function, thus worsening hyperglycemia (glucose toxicity). Moreover, an increase in dietary lipid introduction also worsens islet function (lipotoxicity). In the liver, hyperinsulinemia is no longer able to suppress gluconeogenesis, which results in hyperglycemia and decreased glycogen storage by the liver in the postprandial state [1,2]. Type 2 diabetes is a chronic illness that requires continuing medical care to prevent acute complications and reduce the risk of chronic complications. Diabetes treatment is based on lifestyle interventions, pharmacological therapy and insulin therapy. Lifestyle interventions are strictly recommended for all diabetic patients, particularly for those who present with obesity and insulin-resistance at diagnosis. Medical nutrition therapy is essential to achieve and maintain recommended treatment goals, including FPG, postprandial plasma glucose (PPG), glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels, blood pressure (BP) and body weight. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular (CV) risk factors, contribute to

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weight loss and improve well-being. Before starting a physical activity program, people with diabetes should be evaluated in order to reduce the risk of adverse effects that may possibly occur in subjects with macro- and/or microvascular complications. Advising all patients not to smoke is another important intervention recommended in Type 2 diabetes management. In many cases, optimal glycemic control is not only achieved by changes in lifestyle; most Type 2 diabetic patients requires a pharmacological treatment [3].

Overview of the market

To date, a large number of molecules have been developed to achieve the recommended goals in glycemic control that are strictly related to optimal prevention of Type 2 diabetes complications. The antihyperglycemic agents that are now available include insulin secretagogues (sulphonylureas [SU] and metiglinides), metformin, α -glucosidase inhibitors and thiazolidinediones (TZD). The main features of the different drug classes are presented in Table 1.

Current guidelines suggest and highlight the importance of severe glycemic control in order to prevent diabetic complications.

Owing to its glycemic efficacy, excellent safety profile, low cost as a generic formulation and low incidence of hypoglycemia and weight gain, metformin represents the preferred agent for monotherapy. To date, the main contraindications to metformin are represented by renal impairment, suggested by elevated serum creatinine (>136 mmol/l in men and >124 mmol/l in women) or abnormal creatinine clearance, advanced age (>80 years) and congestive heart failure requiring pharmacological treatment. In the literature, the real contraindications of metformin are controversial, and in case reports, a clear relationship between lactic acidosis and metformin plasmatic levels has not been found. Therefore, it appears difficult to determine the degree to which the drug contributes to this unfavorable condition [4]. Gastrointestinal adverse effects, such as abdominal pain, nausea, dyspepsia, anorexia and diarrhea, are much more common at the start of metformin therapy compared with SUs, although the percentage of patients who undergo discontinuation of metformin after a few weeks is limited [5]. Diarrhea occurring long after the dosage titration period is much less well recognized, but usually requires an immediate period of wash-out [6]. Mild renal impairment and stable heart

failure can no longer be recognized as strong contraindications to the use of metformin [7]. Moreover, the proportion of patients with severe renal impairment among diabetics is, in practice, extremely variable among different populations divided for age, sex, race and comorbidities. A large proportion of patients with Type 2 diabetes have microalbuminuria or overt nephropathy at diagnosis, since diabetes is often present for many years before diagnosis. Screening for microalbuminuria is recommended not only for prevention of nephropathy, but also as a marker of CV morbidity and mortality. Optimal glycemic and blood pressure control is strictly recommended to protect renal function [8].

If metformin is not tolerated or contraindicated, the second choice is between a TZD or a SU. SUs are efficacious and particularly useful in Type 2 diabetic patients who present with insulin secretion deficiency and, in association with insulin-sensitizing drugs (metformin and TZD), in those with Type 2 diabetes mellitus who do not achieve recommended glycemic control.

SUs act at the pancreatic β -cell membrane (SU receptors [SURs]) by determining the closure of adenosine triphosphate (ATP)-sensitive potassium channels. Glimepiride, the later third-generation SU, acts on the same receptors as other SUs, but it is internalized into β -cells, where the molecule is associated with the secretory granules. Glimepiride stimulates the first and the second phases of insulin secretion. Principally, glibenclamide acts at the same SUR as other SUs (a 140 kDa protein) and its metabolism results in long-acting molecules. Thus, this drug can be administered once daily. Glipizide increases the plasma insulin response to food much more than glibenclamide, thus it is more efficacious for postprandial hyperglycemia. Gliclazide increases insulin secretion in the fasting state and after a meal. Among the SUs, glibenclamide produces a higher incidence of hypoglycemia compared with glipizide and glimepiride. In renal insufficiency, the elimination of glimepiride is not changed due to a decrease in protein binding, making this SU a safer option for patients with renal impairment.

A theoretical cardiac risk for first-generation SUs has been observed and appears to be confirmed in studies with glibenclamide. Glimepiride, gliclazide and glipizide have lower affinity for cardiac SURs and, in animal models, glimepiride appears to not impair the protective effect of ischemic preconditioning. To date,

Table 1. The major compounds for the treatment of Type 2 diabetes mellitus.

Compound	Mechanism of action	Site of action	Glycemic efficacy (hba1c)
Sulphonylureas			
2nd generation			
Glibenclamide Glipizide Glipizide GITS Glimepiride	Increase insulin secretion	β -islet cell	1.5–2%
Nonsulphonylureas			
Insulin secretagogues			
Repaglinide Nateglinide	Increase insulin secretion	β -islet cell	0.7–1.3%
Biguanides			
Metformin	Decrease hepatic glucose production and increase peripheral uptake	Liver (muscle and adipose)	1.8%
α-glucosidase inhibitors			
Acarbose Miglitol	Decrease intestinal carbohydrate absorption	Intestine brush border	0.8%
Thiazolidinediones			
Rosiglitazone Pioglitazone	Increase peripheral glucose uptake	Adipose (muscle and liver)	1.5%

GITS: Gastrointestinal therapeutic system.

glimepiride, gliclazide and glipizide appear to be the preferable SUs in Type 2 diabetic patients with coronary disease [9]. However, glimepiride has never been tested in studies of reduction in CV disease compared with other SUs.

Non-SU insulin secretagogues may be used in patients with unpredictable meal schedules and/or those with predominant PPG.

TZDs have demonstrated efficacy not only in glycemic control, but also in the different components of metabolic syndrome (particularly hypertension and dyslipidemia); however, a slow onset of action, a frequent liver enzyme monitoring requirement and association with weight gain do not make these drugs ideal as first agents in Type 2 diabetes treatment. The mechanism of action of TZDs is not well known with regard to their use in patients with Type 2 diabetes and renal impairment. The available evidences suggest a possible beneficial role of these compounds in preventing renal failure and slowing the progression of renal disease. Both rosiglitazone monotherapy and treatment with rosiglitazone in association with SUs has been shown to be well tolerated in Type 2 diabetic patients with mild to moderate renal failure not well controlled by monotherapy. Moreover, in preliminary human studies, rosiglitazone has been demonstrated to

improve glomerular hyperfiltration, renal endothelial dysfunction and microalbuminuria of starting diabetic nephropathy. Different mechanisms, beyond blood pressure reduction and improvement of insulin sensitivity, appear to be involved in this positive effect of rosiglitazone on the kidney. Studies of association of rosiglitazone and SUs have suggested a similar improvement of microalbuminuria excretion rate [10]. α -glucosidase inhibitors as first choice are reserved for those patients with early diagnosed and mild diabetes [11]. Significant outcome data demonstrate that Type 2 diabetes is a progressive condition that requires combination therapy for optimal glycemic control [12].

Lifestyle modification with an oral agent has shown to produce a satisfactory glycemic control for a time that depends on different factors and particularly on patients' adherence to physicians suggestions, as largely stressed by recent recommendations [3]. When hyperglycemia appears no longer adequately controlled, addition of a second agent (not substitution) is recommended. Agents with similar or different mechanisms of action can be combined, with the exception of SU and non-SU insulin secretagogues. The most common combination regimens are: SU plus metformin or TZD; SU plus

TZD; and metformin plus TZD. The availability of fixed combinations has made combination therapy easier to administer [4].

Introduction to rosiglitazone/glimepiride

Chemistry

The fixed combination of glimepiride and rosiglitazone (GlaxoSmithKline) is the combination of two antidiabetic drugs: rosiglitazone maleate and glimepiride. Chemically, rosiglitazone maleate is (\pm) -5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidenedione, (Z)-2-butenedioate (1:1). The molecule has a single chiral center and is present as a racemate. The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone is a white to off-white solid with a melting point range of 122–123°C. The pK_a values are 6.8 and 6.1. Rosiglitazone is readily soluble in ethanol and a buffered aqueous solution with pH 2.3, and solubility decreases with increasing pH in the physiological range (Figure 1).

Glimepiride is a white to yellowish-white, crystalline, odourless powder. Chemically, glimepiride is 1-p-[[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea. The molecular formula of glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water (Figure 1).

A fixed combination of glimepiride and rosiglitazone is available for oral administration. Tablets contain a fixed dose of rosiglitazone 4 mg combined with variable doses of glimepiride 1, 2 or 4 mg (in the US) [101] or rosiglitazone 4 mg combined with glimepiride 4 mg (in the EU) [102].

Pharmacokinetics & metabolism

Glimepiride

After oral administration, glimepiride is absorbed completely (100%) in the gastrointestinal tract. Studies with a single oral dose in healthy subjects and multiple oral doses in Type 2 diabetic patients have shown a significant absorption after 1 h and maximal plasma concentration (C_{max}) at 2–3 h. Glimepiride is metabolized by oxidative biotransformation, thus resulting in the formation of the two main metabolites: cyclohexyl hydroxyl-methyl derivative (M1) and the carboxyl derivative and M2. Glimepiride metabolism involves cytochrome P 450 2C9. The pharmacokinetics of glimepiride are dose linear in the 1–8-mg dose range, safe and well tolerated in healthy volunteers [13,14,101].

Rosiglitazone

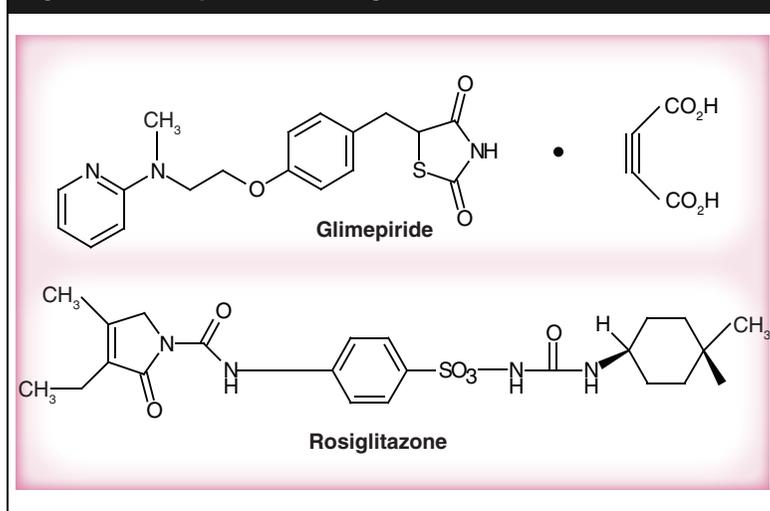
Rosiglitazone is metabolized largely in the liver; its metabolism mainly involves cytochrome P 450 2C8 and, minimally, cytochrome P 450 2C9. The principal metabolites derive from N-demethylation and hydroxylation and successive conjugation with sulphate and glucuronic acid. The elimination half-life is 3–4 h and is independent of the dose. After oral administration, rosiglitazone is absorbed rapidly and its absolute bioavailability is 99%. The pharmacokinetics of rosiglitazone are dose linear in the 4–8-mg dose range. The mean oral volume of distribution of the molecule is approximately 17.9 l and it increases according to body weight. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin [15].

In a bioequivalence study of fixed combination of glimepiride and rosiglitazone 4/4 mg, the area under the curve (AUC) and the C_{max} of rosiglitazone following a single dose of the fixed-combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride 4 mg. Glimepiride AUC was bioequivalent, while glimepiride C_{max} was lowered by 13% when glimepiride was administered in the fixed-dose combination in comparison with glimepiride 4 mg concomitantly administered with rosiglitazone 4 mg (Table 2) [101].

Pharmacodynamics

Glimepiride is the latest second-generation SU for the treatment of Type 2 diabetes mellitus (Table 1). Glimepiride has been shown to improve the relative insulin secretory deficit found in Type 2 diabetes mellitus. It is a direct insulin secretagogue;

Figure 1. Glimepiride and rosiglitazone.



indirectly, it also increases insulin secretion in response to fuels such as glucose. Glimepiride antihyperglycemic efficacy is similar to other secretagogues. It has pharmacokinetic properties that make it safe, with the lowest incidence of hypoglycemia among the SUs. Its convenient once-daily dosing may enhance compliance for diabetic patients who also often require medications for other comorbid conditions. Clinically, its reduced risk of hypoglycemia makes it preferable to some other insulin secretagogues [16].

In comparison with glibenclamide, glimepiride exhibited more potent glucose-lowering effects and a longer duration of its hypoglycemic effect. Glimepiride is indicated in association with diet and exercise for Type 2 diabetes mellitus. Glimepiride in a 1–8-mg daily dose causes a dose-related decrease in blood glucose and glycosylated hemoglobin levels [17]. A large-scale study, conducted under similar conditions to current medical practice, confirms that glimepiride has a favorable risk:benefit ratio in Type 2 diabetes mellitus [18].

Glimepiride appears to be effective in reducing important metabolic risk factors for atherosclerotic vascular disease. In a 12-month study, glimepiride lowered lipoprotein(Lp)a and homocysteine (HCT) levels at 6 and 12 months and plasminogen activator inhibitor Type 1 (PAI-1) at 12 months [19].

Rosiglitazone has a high affinity for the peroxisome proliferators-activated receptor (PPAR)- γ , particular nuclear receptors that have been found in different target tissues, such as liver, skeletal muscle and fat tissue.

Rosiglitazone reduces plasma glucose levels and glucose production and increases glucose clearance in patients with Type 2 diabetes mellitus. Insulin sensitivity, pancreatic β -cell function and surrogate markers of CV risk factors are significantly improved by rosiglitazone. Double-blind trials of 8–26 weeks of rosiglitazone 4 or 8 mg/day monotherapy indicate significant decreases in FPG and HbA1c levels. Efficacy has been maintained in trials of 2 years or less, and has been also apparent in various ethnic subgroups, elderly patients and obese and nonobese patients. Rosiglitazone should be administered in combination with diet and exercise and is generally well tolerated. The incidence of liver function abnormalities in clinical trials (≤ 2 years duration) has been similar to that in placebo and active comparator groups. Fluid retention associated with rosiglitazone may be the cause of the increased incidence of anemia in clinical trials, and also means that patients should be monitored for signs of heart failure during therapy. Although body weight is increased overall with rosiglitazone therapy, increases are in subcutaneous, not visceral fat; hepatic fat is decreased. The pharmacokinetic profile of rosiglitazone is not substantially altered by age or renal impairment, and there are no important drug interactions. Oral rosiglitazone 4 or 8 mg/day provides significant antihyperglycemic efficacy and is generally well tolerated, both as monotherapy and in combination with other antihyperglycemic agents in patients with Type 2 diabetes mellitus without active liver disease [20].

Table 2. Comparison between rosiglitazone plus glimepiride 4/4 mg (regimen A) and concomitant dosing of a rosiglitazone 4 mg tablet plus glimepiride 4 mg tablet (regimen B).

Parameters	Rosiglitazone		Glimepiride	
	R/G 4/4 mg Fixed association	R 4 mg tablet plus G 4 mg tablet	R/G 4/4 mg Fixed association	R 4 mg tablet plus G 4 mg tablet
AUC _{0-inf} (ng.h/ml)	1259 (833–2060)	1253 (756–2758)	1052 (643–2117)	1101 (648–2555)
AUC ₀₋₁ (ng.h/ml)	1231 (810–2019)	1224 (744–2654)	944 (511–1898)	1038 (606–2337)
C _{max} (ng/ml)	257 (157–352)	251 (77.3–434)	151 (63.2–345)	173 (70.5–329)
T _{1/2} (h)	3.53 (2.60–4.57)	3.54 (2.10–5.03)	7.63 (4.42–12.4)	5.08 (1.80–11.31)
T _{max} (h)	1.00 (0.48–3.02)	0.98 (0.48–5.97)	3.02 (1.50–8.00)	2.53 (1.00–8.03)

Adapted from gsk AvandaryTM prescribing information.

AUC: Area under the curve; C_{max}: Maximum concentration; G: Glimepiride; R: Rosiglitazone; T_{1/2}: Time of half-life; T_{max}: Time of maximum concentration.

Treatment with rosiglitazone reduced hyperinsulinemia and improved small artery elasticity with a tendency to improve large artery elasticity in hypertensive and normotensive patients [21]. Rosiglitazone induced a recovery of pancreatic β -cell function, as evidenced by the restoration of the first-phase insulin response to glucose, improvement in the disposition index and a decrease in the proinsulin:insulin ratio in subjects with Type 2 diabetes in whom oral antihyperglycemic therapy failed, independent of the correction of glucotoxicity [22]. In comparison to metformin, rosiglitazone decreases liver fat and increases insulin clearance. The decrease in liver fat is associated with an increase in serum adiponectin concentrations and an increase in peripheral glucose uptake [23]. Rosiglitazone positively affects CV risk markers, producing a reduction in plasmatic concentration of C-reactive protein (PCR), matrix metalloproteinases (MMP)-9, tumor necrosis factor (TNF)- α , seric amyloid and soluble CD40L in Type 2 diabetic patients with and without coronary disease [15].

Clinical efficacy

The efficacy of the fixed combination of glimepiride and rosiglitazone has only been established in studies with the two drugs administered concurrently (Table 3). Evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be more effective in achieving and maintaining target blood glucose levels [12]. In patients with Type 2 diabetes and metabolic syndrome, glimepiride provides slight improvements in cholesterolemia, not observed in rosiglitazone-treated patients [24]. The addition of glimepiride in patients with Type 2 diabetes mellitus who were not adequately controlled by metformin and a TZD dual combination therapy has ameliorated glycemic control compared with placebo, with an acceptable tolerability profile. The risk for severe hypoglycemia increased with the addition of glimepiride [25].

The addition of rosiglitazone to an SU has been shown to improve glycemic control in patients with Type 2 diabetes previously treated with SU monotherapy, and produced a positive effect on insulin resistance, β -cell function, CV risk markers and adiponectin, thus supporting the rationale of combining rosiglitazone with SU drugs in patients with Type 2 diabetes [26].

The association of a TZD to the glimepiride treatment of Type 2 diabetic subjects with metabolic syndrome is associated with a significant

improvement in the long-term blood pressure control, related to a reduction in insulin resistance [27].

Evidence suggests that antihyperglycemic drugs might have a small, but clinically significant, beneficial effect on blood pressure in patients with diabetes mellitus. In a 12-month study, combination treatment with rosiglitazone and metformin, but not glimepiride and metformin, was associated with a significant improvement in blood pressure control. Both treatments were well tolerated [28]. It can be concluded that the addition of a TZD to glimepiride treatment in Type 2 diabetic subjects with metabolic syndrome determines a slight but significant reduction of the PAI-1 value, related to a similar reduction in insulin resistance [29].

Safety & tolerability

Sulphonylureas might determine different adverse events, the most common and important in clinical practice being hypoglycemia. Other SUs, such as glibenclamide, appear to be responsible of severe hypoglycemia more frequently than glimepiride [30].

Another important side effect of glimepiride is weight gain, which is observed with all secretagogues. Rosiglitazone might determine fluid retention and exacerbate heart failure in Type 2 diabetic patients and is not recommended for patients with New York Heart Association (NYHA) class 3 or 4 heart failure [31].

Experts recommend screening for underlying cardiac disease in patients and the use of drugs related to the development of fluid retention of pedal edema, and promptly detect any possible manifestation of chronic heart failure. Moreover, a review of a recent electrocardiogram may be useful to establish the presence of previous myocardial infarction or left ventricular hypertrophy. Finally, experts suggest instructing patients before initiation of treatment regarding onset of symptoms, such as weight gain over 3 kg, pedal edema and dyspnea or fatigue without other particular causes. Correct monitoring must be conducted during therapy [31]. TZDs have been shown to induce weight gain in Type 2 diabetic patients. The weight gain appears to be related to the dose and is nearly 3–6 kg over 6 months to 1 year. Rosiglitazone/glimepiride combination therapy affects weight gain more than rosiglitazone or SU monotherapy [32]; however, weight gain is not inevitable. Combination with sibutramine and orlistat, two well known weight-loss agents, has

Table 3. Metabolic and nonmetabolic effects of the association of glimepiride 4 mg and rosiglitazone 4 mg contemporary administered in five studies.

Compound	HbA1 _c (%)	BMI (kg/m ²)	SBP (mmHg)	DBP (mmHg)	Study duration (weeks)	Ref.
Adiponectin (adjusted for body weight changes): +72.7%						
Glimepiride 3 mg plus rosiglitazone 4 mg	-1.2%	0%	-1.4%	0%	16	[26]
Lipid profile: TC: -3.3 mg/dl; HDL-C: + 0.6mg/dl; TG: -7.5 mg/dl						
Glimepiride 2–8 mg plus rosiglitazone 4–8 mg	-1.2%	No significant changes			26	[37]
Lipid profile: TG: +18%; PAI-1 (ng/ml): -30%; tPA (ng/ml): -26%; Fg (g/l): -10.4%						
Glimepiride 4 mg plus rosiglitazone 4 mg	-1.2%	+7.1%			54	[19]
TC: +14.8%; HDL-C: +2.3%; TG: +18%						
Glimepiride 4 mg plus rosiglitazone 4 mg	-1.3%	+6.2%			54	[19]
Lipid profile: TG: +18%						
Glimepiride 4 mg plus rosiglitazone 4 mg	-1.3%	+6.2%	-3.19%	-5.4%	54	[28]

BMI: Body mass index; DBP: Diastolic blood pressure; Fg: Fibrinogen; HDL-C: High-density lipoprotein cholesterol; PAI: Plasminogen activator inhibitor; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; tPA: Tissue polypeptide antigen.

been shown to be effective in reducing the need for both insulin and secretagogues, although no studies are available concerning the possible effects of these agents in association with TZDs. Weight loss following a low calorie diet is associated with a decrease in PPAR- γ expression in subcutaneous adipose tissue, related to the differentiation of adipocytes. Experts suggest a program of education regarding diet and exercise at prescription, with a restriction in calorie intake, particularly in those patients at high risk of weight gain. Further research is needed to determine optimal and possible standardized dietary modifications during use of TZDs [33]. Moreover, association of TZDs and diuretics seem to be a possible choice to reduce edema during treatment [34]. Diabetic macular edema with rosiglitazone has been reported recently, while hepatotoxicity, a severe adverse effect that has led to the market withdrawal of troglitazone, has been rarely observed with rosiglitazone [35]. These data are consistent with our experience with the association of rosiglitazone and glimepiride [36].

Thus far, no clinical trials have been conducted to assess safety and tolerability of the fixed-dose combination tablet of glimepiride and rosiglitazone as second-line therapy when a SU provides no adequate glycemic control, or in

patients initially responding to rosiglitazone alone who require additional glycemic control.

Safety and efficacy of the fixed combination of glimepiride and rosiglitazone as initial therapy in addition to diet and exercise has also not been established.

The combination of glimepiride and rosiglitazone was efficacious and well tolerated in a small sample of patients with Type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy [37]. In a study designed to test the efficacy and safety of low-dose rosiglitazone in combination with SU in Type 2 diabetic patients, no significant cardiac events, hypoglycemia or hepatotoxicity was observed in the combination-treatment group [38].

In conclusion, the fixed dose of rosiglitazone and glimepiride is contraindicated in patients with known hypersensitivity to one component of the drug, in diabetic ketoacidosis with or without coma. There are no data available evaluating the efficacy and safety of the fixed combination of glimepiride and rosiglitazone in combination with insulin and, therefore, this association is not recommended.

During treatment, periodic FPG and HbA1c measurements should be performed. Liver enzyme monitoring is recommended at the start of prescription and during treatment [101].

Conclusions

To date, the fixed dose of rosiglitazone and glimepiride is indicated in patients with Type 2 diabetes mellitus who are already being treated with a combination of rosiglitazone and SU or who are not adequately controlled on a SU alone, or for those patients who require additional glycemic control after an initial success with rosiglitazone alone.

Management of Type 2 diabetes mellitus should include adequate control of lifestyle [3]. Prior to initiation of the fixed-dose combination of rosiglitazone and SU (fixed combination of glimepiride and rosiglitazone), an appropriate screening of secondary causes of poor glycemic control should be investigated and treated properly.

The fixed combination of glimepiride and rosiglitazone is available for oral administration containing a fixed dose of rosiglitazone 4 mg with variable doses of glimepiride (1, 2 or 4 mg) in a single tablet formulation. The fixed combination of glimepiride and rosiglitazone should be administered once daily with the first meal of the day and dosage should be adapted to singular necessities in order to obtain optimal glycemic control and the lowest incidence of adverse events, particularly severe hypoglycemia and heart failure. The maximum recommended dose is rosiglitazone 8 mg and glimepiride 4 mg. For patients inadequately controlled with SU alone, or who had initially responded to rosiglitazone and require a better glycemic control, recommended starting dose is 4/1 mg (starting dose absolutely recommended in elderly, debilitated and in case of renal, hepatic or adrenal insufficiency) or 4/2 mg. Titration may be performed in those patients who present with impaired physical conditions. When switching to combination therapy from rosiglitazone plus glimepiride as separate tablets, the usual starting dose of fixed combination of glimepiride and rosiglitazone is the dose of rosiglitazone and glimepiride already being taken. Sufficient time should be given to assess the adequacy of the therapeutic response. If hypoglycemia occurs during the titration, the dose of glimepiride may be reduced [101].

More clinical trials are awaited in order to assess the efficacy and real tolerability of the fixed combination of glimepiride and rosiglitazone.

Based on the available data, it is appropriate to conclude that the fixed combination of glimepiride and rosiglitazone is a promising combination treatment useful to improve glycemic control in Type 2 diabetes. Rosiglitazone is an innovative molecule that has demonstrated

efficacy in glycemic control and offers major possibilities to obtain the recommended targets in Type 2 diabetic subjects. Moreover, efficacy goes beyond the positive effect on glycemic metabolism. Rosiglitazone has demonstrated activity to the different components of the metabolic syndrome and in preventing progression from conditions of glucose intolerance of Type 2 diabetes mellitus [39,40]. Moreover, particular attention must be paid to the potential contribution of rosiglitazone in blood pressure control in diabetic patients, particularly in association with glimepiride [27]. Glimepiride is employed largely in clinical practice owing to its good efficacy and relative safety profile. Extensive experience makes this molecule the first choice for those patients who do not present with increased body mass index and are known to have decreased insulin secretion [41]. Experience with combination therapy has provided substantially good results in terms of efficacy and tolerability and is a useful therapeutic strategy in clinical practice. Moreover, the availability of a new formulation combining a fixed dose of a secretagogue and an insulin sensitizer is helpful for those patients who show minimal compliance to oral drugs. In fact, patients with Type 2 diabetes frequently experience the need to assume a multidrug regimen in order to control the different disorders accompanying diabetes mellitus [42].

The possibility of preserving the β -cell function throughout the insulin-sensitizing regimen allows a longer control of hyperglycemia without exogenous insulin employment; concurrently, SU provides earlier control of glycemia, thus avoiding the time required to observe the first signs of rosiglitazone activity (which generally requires nearly 15 days to be manifested) [43].

Five-year view

Emerging evidences stress the necessity of forming strict conditions when defining the optimal diabetes management.

TZDs represent a new strategy to obtain optimal metabolic control and are the first molecules acting directly on the cellular nucleus. The effectiveness of these compounds, in addition to other oral antidiabetic agents, is established, although more data are required to better assess the different applications of TZDs beyond their use in glucose metabolism control. One of the more interesting research fields is the relationship between different pharmacological classes acting on similar substrates: an example is the

overlapping effects of fibrates and TZDs on lipid profiles, which suggests the existence of strictly related mechanisms at the core of metabolic and CV disorders. The potential benefit of the association of rosiglitazone and glimepiride in a combined fixed dose in patients with Type 2 diabetes and mild to moderate renal impairment is an encouraging strategy of pharmacological treatment in subjects not yet compromised enough to be shifted to insulin treatment, but with initial complications.

Many new molecules for Type 2 diabetes mellitus are in development in order to achieve treatment goals earlier in the natural history of the disorder and to maintain a longer glycemic control and reduce adverse effects that frequently lead to a shift to insulin treatment. Exenatide is an incretin mimetic extracted from the Gila monster (a lizard living in the USA). Exenatide stimulates insulin release from β -cells and reduces glucagon concentration in the postprandial state, slowing gastric emptying. It has been approved by the

US FDA for those diabetic patients who do not achieve a good glycemic control with metformin alone or metformin plus an SU. It is not approved in association with insulin treatment and may cause hypoglycemia, vomitus and nausea, less frequently diarrhea, but not weight gain. Exenatide offers a wide range of beneficial glucoregulatory effects, including enhancement of glucose-dependent insulin secretion, restoration of first-phase insulin response, suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying and reduction of food intake [44]. Pramlintide is a synthetic analog of human amylin (produced by β -cells together with insulin). It has been approved by the FDA when insulin treatment is not sufficient. Pramlintide slows gastric emptying, suppresses glucagon postprandial production and gluconeogenesis in the liver and reduces the appetite. It shows the same side effects as exenatide but provokes headache. It does not cause weight gain and may induce hypoglycemia in monotherapy [45,46].

Highlights

- At present, available oral antidiabetic drugs in the market are not sufficient to provide long-term control of hyperglycemia when used as monotherapy.
- New potent drugs, acting on different metabolic disorders present in diabetes, are required to obtain the standards recommended.
- Glimepiride has shown strong efficacy in lowering HbA1c values in a relatively short time, although it does not modify insulin sensitivity, which plays an important role in Type 2 diabetes pathogenesis and influences the other metabolic abnormalities of diabetes.
- Rosiglitazone has shown efficacy in reducing hyperglycemia and improving insulin sensitivity, thus positively affecting other cardiovascular risk factors often associated with diabetes (blood pressure and lipid profile). The combination of rosiglitazone and glimepiride has demonstrated a better glycemic control, without increasing the number of side effects.
- Comorbidity in Type 2 diabetes determines the necessity to employ a number of drugs: this decreases patient adherence to therapy regimen. A fixed-dose compound improves patient compliance to treatment.
- Even if more studies are required, the fixed combination of glimepiride and rosiglitazone is a promising treatment option for diabetic patients who are not well controlled by monotherapy or need a more complete treatment affecting different mechanisms employed in the pathogenesis of diabetes.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Golay A, Ybarra J. Link between obesity and type 2 diabetes. *Best Pract. Res. Clin. Endocrinol. Metab.* 19(4), 649–663 (2005).
2. Kovacs P, Stumvoll M. Fatty acids and insulin resistance in muscle and liver. *Best Pract. Res. Clin. Endocrinol. Metab.* 19(4), 625–635 (2005).
3. American Diabetes Association. Standards in medical care in diabetes. *Diabetes Care* 29(Suppl. 1), S4–42 (2006).
4. McCormack J, Johns K, Tildesley H. Metformin's contraindications should be contraindicated. *CAMJ* 173(5), 502–504 (2005).
5. Derosa G, Ciccarelli L, Piccinni MN *et al.* Rosiglitazone improves insulin resistance parameters in overweight and obese diabetic patients intolerant to metformin. *ISA Abstract book* (2006).
6. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy.* 21(11), 1422–1424 (2001).
7. Holstein A, Egberts EH. Traditional contraindications to the use of metformin – more harmful than beneficial? *Dtsch. Med. Wochenschr.* 131(3), 105–110 (2006).
8. American Diabetes Association. Position statement nephropathy in diabetes. *Diabetes Care* 27(Suppl. 1), S79–S83 (2004).
9. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 64, 1339–1358 (2004).
10. Iglesias P, Diez JJ. Proximosome proliferators activated receptor- γ agonists in renal disease. *Eur. J. Endocrinol.* 154, 613–621 (2006).
11. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 16, 287(3), 360–372 (2002).
12. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement

- for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) group. *JAMA* 281, 2005–2012 (1999).
13. Badian M, Korn A, Lehr KH, Malerczyk V, Waldhausl W. Absolute bioavailability of glimepiride (Amaryl) after oral administration. *Drug Metabol. Drug Interact.* 11(4), 331–339 (1994).
 14. Malerczyk V, Badian M, Korn A, Lehr KH, Waldhausl W. Dose linearity assessment of glimepiride (Amaryl) tablets in healthy volunteers. *Drug Metabol. Drug Interact.* 11(4), 341–357 (1994).
 15. Wellington K. Rosiglitazone/metformin. *Drugs* 65(11), 1581–1592 (2005).
 16. McCall AL. Clinical review of glimepiride. *Expert Opin. Pharmacother.* 2(4), 699–713 (2001).
 17. Becic F, Kapic E, Becic E. Glimepiride – an oral antidiabetic agent. *Med. Arb.* 57(2), 125–127 (2003).
 18. Charpentier G, Vaur L, Halimi S *et al.* DIAMETRE. Predictors of response to glimepiride in patients with type 2 diabetes mellitus. *Diabetes Metab.* 27(5 Pt 1), 563–571 (2001).
 19. Derosa G, Franzetti I, Gadaleta G, Ciccarelli L, Fogari R. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin. *Diabetes Nutr. Metab.* 17(3), 143–150 (2004).
 20. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 62(12), 1805–1837 (2002).
 21. Shargorodsky M, Wainstein J, Gavish D, Leibovitz E, Matas Z, Zimlichman R. Treatment with rosiglitazone reduces hyperinsulinemia and improves arterial elasticity in patients with type 2 diabetes mellitus. *Am. J. Hypertens.* 16(8), 617–622 (2003).
 - **Rosiglitazone positively affects endothelium, thus preventing atherosclerosis damages.**
 22. Ovalle F, Bell DS. Effect of rosiglitazone versus insulin on the pancreatic β -cell function of subjects with type 2 diabetes. *Diabetes Care* 27(11), 2585–1589 (2004).
 23. Tiikkainen M, Hakkinen AM, Korshennikova E, Nyman T, Makimattila S, Yki-Jarvinen H. Diabetes effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes* 53(8), 2169–2176 (2004).
 24. Derosa G, Gaddi AV, Piccinni MN *et al.* Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. *Diabetes Obes. Metab.* 8(2), 197–205 (2006).
 25. Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin. Ther.* 27(10), 1535–1547 (2005).
 26. Pfutzner A, Schondorf T, Seidel D *et al.* Impact of rosiglitazone on β -cell function, insulin resistance, and adiponectin concentrations: results from a double-blind oral combination study with glimepiride. *Metabolism* 55(1), 20–25 (2006).
 27. Derosa G, Cicero AF, Dangelo A *et al.* Thiazolidinedione effects on blood pressure in diabetic patients with metabolic syndrome treated with glimepiride. *Hypertens Res.* 28(11), 917–924 (2005).
 28. Derosa G, Cicero AF, Gaddi AV *et al.* Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. *Clin. Ther.* 27(9), 1383–1391 (2005).
 29. Derosa G, Cicero AF, Gaddi A *et al.* A comparison of the effects of pioglitazone and rosiglitazone combined with glimepiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome. *Diabetes Res. Clin. Pract.* 69(1), 5–13 (2005).
 - **Interesting study that highlights the many anti-inflammatory and antiatherosclerotic effects of rosiglitazone.**
 30. Szoke E, Gosmanov NR, Sinkin JC *et al.* Effects of glimepiride and glyburide on glucose counterregulation and recovery from hypoglycaemia. *Metabolism* 55(1), 78–83 (2006).
 31. Nesto RW, Bell D, Donow RO *et al.* Thiazolidinediones, fluid retention and congestive heart failure. *Diabetes Care* 27, 256 (2004).
 32. Hussein Z, Wentworth JM, Nankervis AJ, Proietto J, Colman PJ. Effectiveness and side effects of thiazolidinediones for type 2 diabetes: real-life experience from a tertiary hospital. *Med. J. Aust.* 181, 326 (2004).
 33. Fonseca V. Effect of thiazolidinediones on body weight in patients with type 2 diabetes mellitus. *Am. J. Med.* (115), 42S–48S (2003).
 34. Mudaliar S, Chang AR, Henry RR. Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications. *Endocr. Pract.* 9(5), 406–416 (2003).
 35. The Medical Letter on Drugs and Therapeutics. 48, 1230 (2006).
 36. Derosa G, Cicero AFG, Gaddi A *et al.* Metabolic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and metabolic syndrome treated with glimepiride: a twelve month, multicenter, randomized, controlled, parallel group trial. *Clin. Ther.* 26(5), 744–754 (2004).
 37. McCluskey D, Touger MS, Melis R, Schleusener DS, McCluskey D. Results of a randomized, double-blind, placebo-controlled study administering glimepiride to patients with type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy. *Clin. Ther.* 26(11), 1783–1790 (2004).
 38. Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients. *ACP J. Club* 133(2), 49 (2000).
 39. Home P, Gubb J, for the RECORD study steering committee and investigators. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD): a long-term cardiovascular outcome study. *Diabetes* 51(Suppl. 2), A487 (2002).
 40. Hung YJ, Hsieh CH, Pei D *et al.* Rosiglitazone improves insulin sensitivity and glucose tolerance in subjects with impaired glucose tolerance. *Clin. Endocrinol.* 62(1), 85–91 (2005).
 41. Korytkowski MT. Sulfonylurea treatment of type 2 diabetes mellitus: focus on glimepiride. *Pharmacotherapy* 24(5), 606–620 (2004).
 42. Bell DS. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clin. Ther.* 26(11), 1714–1727 (2004).
 43. Dailey G. Insulin secretagogues: who, what, when, and how? *Curr. Diab. Rep.* 5(5), 329–332 (2005).
 44. Triplitt C, Chiquette E. Exenatide: from the Gila monster to the pharmacy. *J. Am. Pharm. Assoc.* 46(1), 44–52 (2006).

45. Ryan GJ, Jobe LJ, Martin R. Pramlintide in the treatment of type 1 and type 2 diabetes mellitus. *Clin. Ther.* 27(10), 1500–1512 (2005).
46. Young A. Tissue expression and secretion of amylin. *Adv. Pharmacol.* 52, 19–45 (2005).

Websites

101. US FDA prescribing information (US)
US.gsk.com/product/assets/us_avandaryl.pdf.
101. GSK Avaglim Summary of product Characteristics (EU)
www.emea.eu.int/humandocs/PDFs/EPAR/avaglim/H-675-PI-en.pdf

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