

Rosiglitazone and glimeperide: review of clinical results supporting a fixed dose combination

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Abstract: Type 2 diabetes has become a major burden to the health care systems worldwide. Among the drugs approved for this indication, glimepiride and rosiglitazone have gained substantial importance in routine use. While glimepiride stimulates β -cell secretion and leads to reduction of blood glucose values, rosiglitazone activates PPAR γ and improves insulin resistance, at the vascular and metabolically active cells. Therefore, the combination of the two drugs may be an interesting approach to improve glycemic control and lower cardiovascular risk. A fixed combination of both drugs has been approved for clinical use in the US and EU. The combination of glimepiride and rosiglitazone is generally well tolerated and the use of a fixed combination may lead to improved adherence of the patients to their therapy. The purpose of this review is to evaluate the clinical data that have been published on this combination, appearing to represent a convenient way to obtain therapeutic targets in patients with type 2 diabetes mellitus.

Keywords: rosiglitazone, glimepiride, thiazolidinediones, sulfonylurea, combination

Introduction

Type 2 diabetes is a leading cause of morbidity and mortality in many countries and the number of cases is currently approaching pandemic proportions (Zimmet et al 2001). Patients with both types of diabetes mellitus have an increased risk of fatal cardiovascular events. About 75% patients with type 2 diabetes die from macrovascular complications, but only 35% of the patients with type 1 diabetes. This significant difference is linked to insulin resistance and β -cell dysfunction, the underlying disorders in type 2 diabetes (Pickup and Williams 2002). Insulin resistance leads to increased β -cell activity, and the impairment of β -cell function is followed by a deterioration of the β -cell secretion product, leading to secretion of the insulin precursor proinsulin. While proinsulin has only about 10%–20% of the blood-glucose-lowering activity of insulin, it has comparable effects on the induction of adipogenesis (Pfützner et al 2006b). The consecutive growth of adipose tissue, however, is accompanied by a hormonal secretion pattern that impairs insulin resistance (Figure 1). With advancing disease progression, even more proinsulin is secreted, which is known to contribute to the increased cardiovascular risk by inducing plasminogen activator inhibitor type-I (PAI-I) secretion, consecutively leading to an impairment of fibrinolysis (Schneider et al 1992; Pfützner et al 2004).

Different treatment moieties are available to address these pathophysiological components of type 2 diabetes. The first attempt in primary care is usually to treat the patients with a combined approach of increased physical activity and dietary recommendations, which should be accompanied by patient training about the disease in order to increase the adherence to the required lifestyle changes. However in daily routine, lifestyle modifications are not consequently followed and a progressive deterioration of blood glucose metabolism leading to increased hemoglobin A1c (HbA1c) values requires the introduction of oral anti-diabetic agents. At this stage, several therapeutic options

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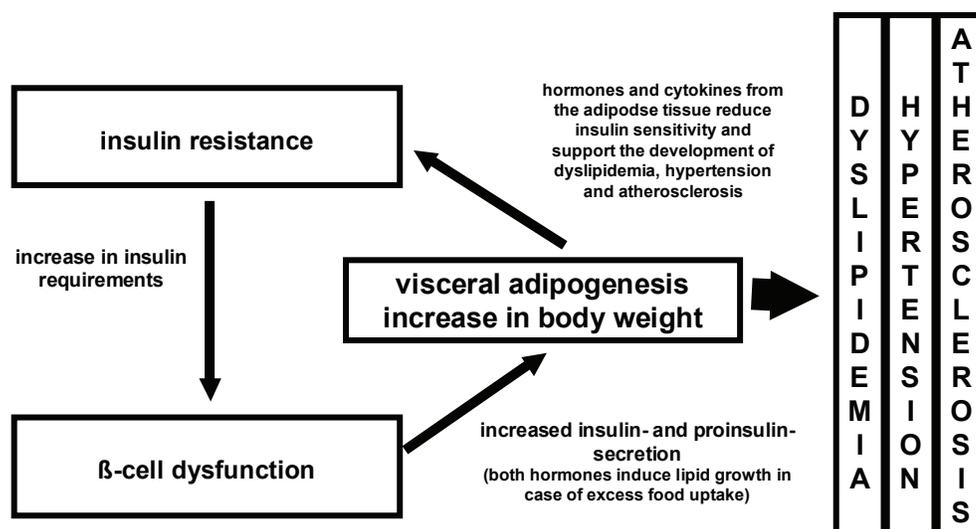


Figure 1 The relation of insulin resistance, β -cell dysfunction, obesity, and their associated complications.

are available including metformin, sulfonylurea drugs (SU), thiazolidinediones, alpha-glucosidase inhibitors, and injectable or pulmonary insulin. While it would directly address β -cell dysfunction, insulin is not frequently used for therapy initiation because patients do not want to inject and the therapy is also not recommended as first-line approach for economic reasons in many countries. The price of the drugs may also be the reason for the more hesitant use of thiazolidinediones (TZD) in initial diabetes mono-therapy. The currently most frequently prescribed drugs for first-line treatment are the SUs and metformin. In many therapeutic guidelines, metformin is recommended for obese patients while use of SUs is suggested in patients with normal or slightly increased body weight (American Diabetes Association 2006).

With the currently predominantly used therapies, type 2 diabetes appears to be a constantly progressing disease and mono-therapy may last for approximately 5–10 years before a further increase in HbA1c indicates the requirement of more intensive treatment regimens. At this stage, a second oral anti-diabetic drug will be introduced to increase the efficacy of the therapeutic approach. One approach may be the combination of SU and TZD in order to benefit from the synergistic therapeutic actions of both drug classes.

Rationale for the combination

Glimepiride [1-p-[[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulphonyl]-3-(trans-4-methylcyclohexyl) urea] is a sulfonylurea drug that stimulates β -cell secretion by binding to a 65 kDa β -cell

receptor leading to a decrease in gluco/hexokinase binding to porin proteins and an increase in the expression of glukokinase mRNA. The chemical structure is shown in Figure 2. The largest effects appear during the first 4 hours after uptake and doses of 1–8 mg are usually given before or with breakfast. The extra-pancreatic effects seem to be similar to those of other SUs (McCall AL 2001). The unfavorable cardiovascular effects of SUs, eg, increase in diazoxide-induced K_{ATP} -channel opening, ST segment changes, and blood pressure increase, are less pronounced with glimepiride than with glibenclamide (Langtry and Balfour 1998). By increasing β -cell output, glimepiride lowers blood glucose levels and HbA1c, the major treatment targets in the management of type 2 diabetes. Recent investigations describe an additional PPAR γ -stimulating effect of glimepiride and an induction of endothelial NO synthesis, which makes glimepiride the most interesting SU candidate for a combination with TZDs (Fukuen et al 2005; Ueba et al 2005).

A lifestyle change with regular performance of physical exercise and weight loss would be a normal and physiological way to improve insulin resistance, the second component of the underlying pathophysiology. The only drug class effectively addressing this condition is the class of thiazolidinediones or PPAR γ -agonists, with two currently commercially available drugs, pioglitazone and rosiglitazone. The chemical structure of rosiglitazone [(±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy] phenyl] methyl]-2, 4-thiazolidenedione, (Z)-2-butenedioate (1:1)] is also shown in Figure 2. TZDs activate the nuclear

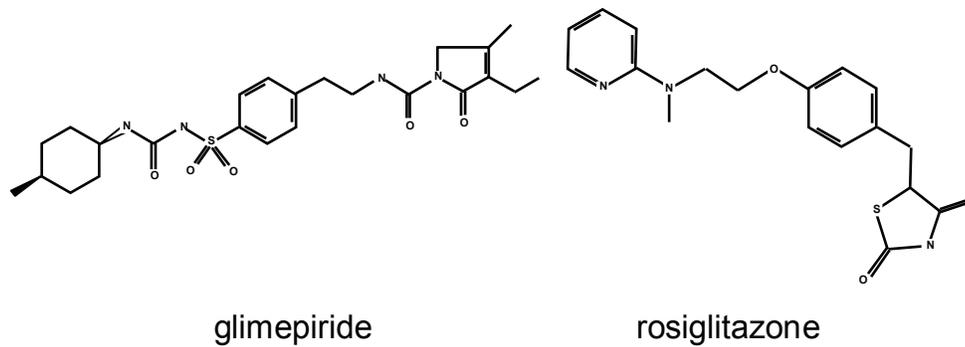


Figure 2 Chemical structures of glimepiride and rosiglitazone.

peroxisome proliferator-activated receptor (PPAR) γ , which is expressed predominately in adipose tissue and regulates the gene transcription involved in adipocyte differentiation and glucose and lipid metabolism (Kersten et al 2000; Schoonjans et al 2000; Debril et al 2001). The metabolic effects of PPAR γ activation by rosiglitazone comprise an increase in peripheral insulin sensitivity in muscle, liver, and adipose tissue (Hallsten et al 2002; Wagstaff et al 2002), improvement of postprandial and fasting glucose concentrations as well as long-term glucose control, improvement of adipogenesis leading to an increase in HDL cholesterol (Wagstaff et al 2002), reduction of vascular inflammation (Natali et al 2004), improvement of arterial elasticity (Shargorodsky et al 2003), and a reduction of laboratory markers for cardiovascular risk (Haffner et al 2002; Marx et al 2003a, b; Mohanty et al 2004; Pfützner et al 2006a).

The rationale for the fixed combination is the synergistic effect of both substances via different modes of action on elevated blood glucose levels and the potential that the observed anti-inflammatory effects of rosiglitazone at the vascular level may correct the expected negative influence of a SU on the chronic vascular inflammation.

Efficacy and tolerability of the fixed combination of glimepiride and rosiglitazone

The fixed combination of rosiglitazone has only recently been approved for clinical use. The idea of manufacturing a fixed combination of rosiglitazone with a sulfonylurea drug came from the results of past clinical trials performed with the drugs given as separate tablets. An overview of the important published studies on this topic is provided in Table 1.

Studies comparing the rosiglitazone/SU combination vs SU mono-therapy

While the benefit of adding rosiglitazone to sulfonylurea drugs was initially shown several years ago vs continuation of the pre-existing therapy in European, American, and Asian patients (Wolffenbüttel et al 2000; Vongthavarat et al 2002; Yang et al 2003; Zhu et al 2003), a series of controlled clinical trials compared the addition of rosiglitazone to different sulfonylureas at a low dose (glibenclamide, gliclazide, glipizide, and glimepiride) with the up-titration of the respective SU drugs in patients at early disease stages (see below).

Kerenyi et al (2004) compared the efficacy of a daily combination of 8 mg of rosiglitazone with 7.5 mg glibenclamide vs the up-titration of the SU, in a total of 340 patients with inadequately controlled type 2 diabetes (FPG ≥ 7.0 and ≤ 15.0 mmol/L) on glibenclamide 7.5 mg/day. They were randomized to either additional treatment with rosiglitazone 8 mg/day or up-titration of the glibenclamide dose (maximum dose = 15 mg/day) for an observation period of 26 weeks. Treatment with the rosiglitazone/SU combination reduced HbA1c by 0.91% and FPG by 2.4 mmol/L (intensified glibenclamide mono-therapy: HbA1c: -0.14%, FPG: +0.2 mmol/L, both $p < 0.001$ compared with the combination). With the rosiglitazone/SU combination, an increase in HDL cholesterol by 15.8% and a decrease in free fatty acids by 15.3% and triglycerides by 5.8% could be observed. Both treatments were well tolerated and had predictable safety profiles, which led to the final conclusion that addition of rosiglitazone provided significantly improved glycemic control compared with up-titration of glibenclamide (Kerenyi et al 2004).

A second study investigated the TZD/SU combination with gliclazide as the SU component. A total of 471 patients with type 2 diabetes who were inadequately controlled on a

Table 1 Overview on the clinical studies applying a combination of rosiglitazone and a SU drug in comparison with uptitration of the SU in patients failing on low dose SU therapy

Combination Rosiglitazone+	Size and duration	Results	References
Rosiglitazone addition Glipizide	n = 340 26 weeks	Better HbA1c and FPG with the combination vs uptitration of glipizide alone. More hypoglycemic events and mild edema with the combination. Patients with the combination gained significantly more weight than with SU alone.	Kerenyi et al 2004
Gliclazide	n = 471 26 weeks	Better HbA1c and FPG with the combination vs uptitration of gliclazide alone. More hypoglycemic events and oedema with the combination. Patients with the combination gained significantly more weight than with SU alone.	Baksi et al 2004
Glibenclamide	n = 227 2, years	Better HbA1c and FPG with the combination vs uptitration of glibenclamide alone. Comparable incidence of hypoglycaemic events. More mild oedema with the combination.	Rosenstock et al 2005 Herzman et al 2005
Glimepiride	n = 391 30 weeks	Patients with the combination gained significantly more weight than with SU alone. Better HbA1c and FPG with the combination vs uptitration of glimepiride alone. More hypoglycaemic events and mild oedema with the combination. Patients with the combination gained significantly more weight than with SU alone.	Rosenstock et al 2005
Glimepiride	n = 174 26 weeks	Better HbA1c and FPG with the combination (with uptitration of rosiglitazone) vs glimepiride alone. Improvement of inflammatory risk markers, insulin resistance and β -cell function in the rosiglitazone arms only. Comparable incidence of hypoglycemic events. More mild edema with the combination. Patients with the 8 mg combination gained significantly more weight than with SU alone.	Hamann et al 2003 Pfützner et al 2006a
Glimepiride addition Glimepiride	n = 40 26 weeks	Better HbA1c and FPG with the combination in patients failing on rosiglitazone monotherapy. No increase in hypoglycemic episodes or other adverse events.	McCluskey et al 2004

Abbreviations: FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SU, sulfonylurea.

half-maximal dose of gliclazide (160 mg/day) were randomized to receive either the addition of rosiglitazone (4 mg bid) or to have their gliclazide uptitrated to a maximum of 320 mg/day during a 26-week treatment period. A reduction in HbA_{1c} of 1.3% ($p < 0.001$) was observed in the combination treatment group compared with the uptitrated gliclazide at endpoint. The proportion of patients who achieved an HbA_{1c} value $< 7\%$ was also greater in the combination group (48% vs 22%). FPG was reduced by 3.0 mmol/L ($p < 0.001$) in the rosiglitazone/SU group compared with the uptitrated gliclazide group after 26 weeks. The observed side-effects included an increased incidence of signs or symptoms suggestive of hypoglycemia with rosiglitazone/SU compared with uptitrating the gliclazide dose (6% vs 2%). Only 1% of patients reported severe hypoglycemia. The combination treatment led to increases in plasma lipoproteins, and more patients experienced edema (11% vs 3%). A significant increase in body weight was observed in patients receiving rosiglitazone plus gliclazide vs uptitrated gliclazide (3.4 kg; $p < 0.001$). The authors concluded that the addition of rosiglitazone (4 mg bid) to gliclazide (160 mg/day) was well tolerated, and significantly more effective in improving glycemia than uptitrating gliclazide to 320 mg/day (Baksi et al 2004).

The aim of a recently published study (Rosenstock et al 2005) in older patients with type 2 diabetes was to compare the efficacy, safety, and tolerability of adding rosiglitazone vs glipizide dose escalation when the patients were inadequately controlled on low dose SU therapy. A total of 227 patients (age: > 60 years) were randomized to receive rosiglitazone (4 mg) or placebo once daily in combination with glipizide 10 mg twice daily for 2 years in a double-blind, parallel-group study design. Treatment options were individualized, and escalation of study medication was specifically defined. Disease progression, defined as the time to reach confirmed FPG > 10 mmol/L while on maximum doses of both glipizide and study medication or placebo, was reported in 28.7% of patients uptitrating glipizide plus placebo compared with only 2.0% taking rosiglitazone and glipizide combination ($p < 0.001$). The combination significantly decreased HbA_{1c}, FPG, insulin resistance, and plasma free fatty acids. The authors concluded that the addition of rosiglitazone to SU in older patients with type 2 diabetes significantly improved glycemic control and reduced disease progression compared with uptitrated glipizide alone and without increasing hypoglycemia. These benefits were associated with increased patient treatment satisfaction and reduced medi-

cal care utilization in terms of emergency room visits and length of hospitalization (Herman et al 2005; Rosenstock et al 2005).

The purpose of a fourth clinical trial (Rosenstock et al 2006b), a 24-week, randomized, double-blind, controlled study, was to demonstrate that the early addition of rosiglitazone to submaximal therapeutic doses of glimeperide leads to greater glycemic improvement than uptitration of glimeperide to maximal dose. Prior to study entry, subjects were treated with a single oral agent or low-dose oral combination therapy. Mean duration of diabetes was approximately 5 years in the two treatment groups. All subjects received low-dose glimeperide (2 mg) during a 6-week run-in period. At randomization, subjects either added 4 mg of rosiglitazone to the glimeperide dose (add-on group) or added placebo to an increased glimeperide dose (4 mg, uptitration group) once daily. After 8 weeks, glimeperide was increased to 4 mg in the rosiglitazone add-on group ($n = 180$) or to 8 mg in the glimeperide uptitration group ($n = 181$), if fasting blood glucose was ≥ 110 mg/dL. While no change from baseline in HbA_{1c} or FPG was observed in the uptitration group (-0.08% ; -0.6 mg/dL, not significant in both cases), a significant reduction in both observation parameters was seen in the rosiglitazone add-on group (-0.68% ; -27.7 mg/dL; $p < 0.05$ in both cases and between groups). In this study, the addition of rosiglitazone to low-dose glimeperide led to clinically and statistically significant decreases in HbA_{1c} and FPG levels compared with uptitration of glimeperide alone, and more subjects reached the ADA goal of HbA_{1c} $< 7\%$ (63.9% vs 39.8%, $p < 0.05$). Addition of rosiglitazone also showed significant improvements in HOMA β -cell function (18%) and insulin sensitivity (15%) estimates relative to glimeperide alone ($p < 0.05$). Both therapies were well tolerated. The incidence of hypoglycemia with blood glucose ≤ 50 mg/dL was low and similar between the groups. The authors concluded that their study supported the paradigm that early introduction of oral combination therapy is more effective in achieving glycemic control than increasing doses of SU mono-therapy, without increasing the risk of confirmed hypoglycemia (Rosenstock et al 2006b).

In another randomized double-blind parallel study with patients with type 2 diabetes, 3 mg of glimeperide was used as a baseline therapy in all treatment groups. Based on the randomization scheme, the patients received additional treatment with placebo (group 0), 4 mg (group 4), or 8 mg (group 8) of rosiglitazone for 4 months. The investigation was performed to assess efficacy and safety of the rosiglitazone/glimeperide combination therapy (HbA_{1c}, FPG, hypoglycemia, and

adverse events). The combination of 4 mg or 8 mg of rosiglitazone with glimepiride 3 mg significantly improved glycemic control compared with glimepiride alone. HbA1c levels were significantly reduced from baseline in group 4 by -0.63% and group 8 by -1.17% , but not in group 0 (-0.08% , $p < 0.001$ vs both other groups). FPG was significantly reduced in group 8 vs group 0 ($p < 0.001$) and a greater proportion of patients treated with the combination achieved target levels of HbA1c (ADA goal of HbA1c $<7\%$: group 4: 43%; group 8: 68% vs group 0: 32%). Mean body weight increased in group 8 by 1.7 kg ($p < 0.01$ vs baseline), whereas the weight gain with the lower rosiglitazone dose was not significantly different from that with the glimepiride mono-therapy arm. All treatments were generally well tolerated with no significant differences in the incidence or profile of adverse events between the treatment groups. There were no withdrawals due to hypoglycemia, hepatotoxicity, or edema. In particular, combination treatment did not increase the incidence of hypoglycemia compared with glimepiride alone (Hamman et al 2003).

For a subgroup of 102 patients (group 0: $n = 30$; group 4: $n = 31$; group 8: $n = 41$; 46 women, 56 men, mean age: 62.8 ± 9.1 years, BMI 28.7 ± 4.5 kg/m², diabetes duration 6.4 ± 4.8 years, HbA1c $8.1 \pm 1.5\%$), additional samples were available from this study for assessment of HOMA_{IR} score, insulin, intact proinsulin, and adiponectin after 0 and 16 week of treatment. Insulin resistance was defined by elevated intact proinsulin values or HOMA_{IR} >2 . All parameters were comparable in the three groups at baseline. While no changes were seen for any of the observation parameters except an increase in adiponectin from 8.4 ± 5.1 mg/L to 11.9 ± 6.2 mg/L ($+42\%$, $p < 0.001$) with glimepiride alone, substantial and significant dose-dependent improvements were observed after addition of rosiglitazone for fasting glucose (group 0: -9 ± 48 mg/dL; group 4: -38 ± 47 mg/dL; group 8: -46 ± 53 mg/dL), HbA1c ($-0.1 \pm 0.7\%$; $-1.1 \pm 1.2\%$; $-1.3 \pm 1.2\%$), insulin ($+1.4 \pm 6.2$ μ U/mL; -1.2 ± 5.3 μ U/mL; -3.7 ± 9.9 μ U/mL), and intact proinsulin ($+1.6 \pm 7.1$ pmol/L; -2.0 ± 4.6 pmol/L; -3.1 ± 6.1 pmol/L). After adjustment for changes in body weight, a significant additional contribution of PPAR γ activation ($p < 0.001$) to the adiponectin increase was detected, while glimepiride alone did not induce a comparable effect (-0.5 ± 5.8 mg/L; $+8.8 \pm 22.9$ mg/L; $+14.3 \pm 19.9$ mg/L). The number of insulin-resistant patients decreased in both rosiglitazone treatment groups, while no change was seen with glimepiride alone. Next to the reported effects on glucose control, rosiglitazone provided an additional beneficial effect on insulin resistance and β -cell function leading to

lower HOMA_{IR} scores, lower values for insulin, and intact proinsulin, and a more pronounced increase in adiponectin values. These results supported the clinical rationale of combining rosiglitazone with sulfonylurea drugs in patients with type 2 diabetes (Pfützner et al 2006a).

In accordance with the current treatment guidelines, rosiglitazone was added to a SU drug in all aforementioned trials, but McCluskey et al (2004) investigated the converse situation. A total of 40 patients who failed on rosiglitazone mono-therapy were treated with additional glimepiride vs placebo for 26 weeks. The outcomes were greater reductions for the glimepiride vs the placebo combination in HbA1c (mean [SE], -12% [0.1%] vs -3% [2%]; $p < 0.001$) and FPG (mean [SE], -24.4 [6.0] mg/dL vs 5.9 [8.0] mg/dL; $p < 0.01$). More patients in the glimepiride group achieved the HbA1c target of $\leq 7\%$ (60% vs 14%; $p < 0.01$). There were no significant differences in the rate or type of adverse events between groups, and no episodes of severe hypoglycemia occurred with either treatment (McCluskey et al 2004). It needs to be pointed out, however, that the inclusion criteria of the patients in this trial may have potentially resulted in selection of pharmacological non-responders to rosiglitazone therapy, but unfortunately no pharmacogenetic characterization is provided for the trial participants in this manuscript.

Addition of pioglitazone (15 mg) or rosiglitazone (4 mg) to glimepiride in patients with type 2 diabetes and metabolic syndrome for 12 months in a double-blind randomized parallel trial resulted in a comparable reduction in HbA1c and FPG with both drugs, comparable improvement of insulin resistance and the prothrombotic state, but with better lipid values resulting from the pioglitazone/glimepiride combination. In general, however, the overall efficacy and side-effect profiles of both TZD/SU combinations were considered to be beneficial for the metabolic control of the patients (Derosa et al 2004 and 2005a).

In summary, all these dual combination trials have demonstrated that the use of rosiglitazone together with sulfonylurea drugs provides a better glycemic control compared with further intensifying the SU mono-therapy. This result was accompanied by an improvement in the cardiovascular risk profile of the patients. The metabolic improvements were associated with an equal or increased number of hypoglycemic events. However, this increase in hypoglycemia needs to be analyzed in the context of the observed parallel HbA1c improvements. Other observed side-effects of the TZD/SU combination vs SU alone were increases in body weight and an increased incidence of mild edema, which are established

side-effects of rosiglitazone therapy. The combination was well tolerated and no indications of hepatotoxicity were observed in any of the trials.

Studies of rosiglitazone/SU in other treatment combinations

In the past, the usual oral combination to be prescribed after failure of SU or metformin mono-therapy was the combination of SU with metformin. Some studies have investigated the combination of rosiglitazone with metformin vs metformin/SU (eg, Derosa et al 2005b, 2006), but no investigation is available comparing rosiglitazone/glimepiride with the metformin/SU combination. In comparison with metformin, rosiglitazone decreases liver fat and increases peripheral glucose uptake. The decrease in liver fat is associated with an increase in serum adiponectin concentrations (Tiikainen et al 2004). Rosiglitazone positively affects CV risk markers, reducing plasmatic concentration of C-reactive protein (PCR-), matrix metallo-proteinases (MMP-9), tumor necrosis factor-alpha (TNF-alpha), serum amyloid, and soluble CD40L in type 2 diabetic patients with and without coronary disease (Wellington 2005). These effects seem to be conserved when rosiglitazone is used in combination with glimepiride (Pfützner et al 2006a) and both drugs are, therefore, interesting candidates also for multiple component therapies, especially when a fixed-dose combination of rosiglitazone and glimepiride may help to reduce the number of daily tablets.

Orbay et al (2004) investigated the addition of rosiglitazone to a combination of glimepiride and metformin therapy in patients with insufficiently controlled type 2 diabetes over 26 weeks. Thirty patients were taking glimepiride (3 mg) and metformin (850 mg) two times per day and added rosiglitazone (4 mg) before breakfast. Mean HbA1c levels decreased significantly from $7.54 \pm 0.9\%$ to $6.57 \pm 0.7\%$ ($p < 0.001$) and FPG levels fell from 169 ± 38 mg/dL to 136 ± 28 mg/dL ($p < 0.001$), respectively. Insulin levels decreased from 19.6 ± 9.8 U/L to 14.7 ± 11.6 U/L ($p < 0.05$) at endpoint. No elevations of alanine aminotransferase or aspartate aminotransferase levels greater than 2.5 times the upper limit of the reference range were observed. This study confirmed that the addition of rosiglitazone (4 mg/day) to SU and metformin treatment may provide a promising approach to achieve target levels of glycemia (Orbay et al 2004).

A different study by Roberts et al (2005) evaluated the efficacy and tolerability of glimepiride in patients with type 2 diabetes mellitus that were inadequately controlled with a combination of immediate- or extended-release metformin and a thiazolidinedione. In this multicenter, randomized,

double-blind, placebo-controlled, parallel-group, 2-arm study consisting of a 4-week stabilization and eligibility period and a 26-week treatment period, 170 patients with type 2 diabetes received glimepiride (uptitration possible) or placebo in combination with an established regimen of immediate- or extended-release metformin and rosiglitazone or pioglitazone. Demographic variables were similar at baseline between the glimepiride and placebo groups. HbA1c was significantly improved at endpoint with glimepiride combination therapy compared with placebo (mean [SE], -1.31% [0.08] vs -0.33% [0.08], respectively; $p < 0.001$). Most patients (62.2%) who received glimepiride achieved an HbA1c value of $\leq 7\%$, compared with 26.0% of patients receiving placebo ($p < 0.001$ between groups). Patients on glimepiride therapy had a higher BMI at endpoint (adjusted change from baseline to endpoint 1.26 ± 0.16 kg/m² with glimepiride and 0.17 ± 0.16 kg/m² with placebo ($p < 0.001$). There were no significant differences in lipid levels between groups. Clinically significant adverse events, laboratory abnormalities, and rates of severe hypoglycemia were similar between treatment groups. The overall incidence of hypoglycemia, however, was 51.2% in the glimepiride group and 8.3% in the placebo group ($p < 0.001$). This study showed that in these patients with type 2 diabetes not adequately controlled by dual combination therapy with metformin and a thiazolidinedione, the addition of glimepiride improved glycemic control compared with placebo with an acceptable tolerability profile. Although there were significantly more episodes of hypoglycemia with triple therapy than with dual therapy and placebo, the risk for severe hypoglycemia was low. This study again supports the use of glimepiride in conjunction with TZD combination therapies (Roberts et al 2005).

A controlled study investigating the effects of adding rosiglitazone in comparison to a long acting insulin analogue on metabolic control in patients inadequately controlled with a metformin/SU combination therapy was recently published by Rosenstock et al (2006b). In this 24-week multicenter, randomized, open-label, parallel trial, 217 patients (HbA1c: 7.5%–11%, BMI > 25 kg/m²) on $\geq 50\%$ of maximal-dose SU and metformin received add-on insulin glargine 10 units/day or rosiglitazone 4 mg/day. Insulin glargine was forced-titrated to target FPG (≤ 100 – 120 mg/dL), and rosiglitazone was increased to 8 mg/day any time after 6 weeks, if FPG was > 5.5 mmol/L. A similar improvement in HbA1c was observed in both groups (-1.7% vs -1.5% for insulin glargine vs rosiglitazone, respectively). When baseline HbA1c was $> 9.5\%$, the reduction with insulin glargine was

greater than with rosiglitazone ($p < 0.05$). Also, insulin glargine yielded better FPG values than rosiglitazone (-3.6 ± 0.23 mmol/L vs -2.6 ± 0.22 mmol/L; $p < 0.001$). The final daily insulin glargine dose was 38 ± 26 IU vs 7.1 ± 2 mg for rosiglitazone. Confirmed hypoglycemic events at plasma glucose <3.9 mmol/L (<70 mg/dL) were slightly greater for the insulin glargine group ($n = 57$) than for the rosiglitazone group ($n = 47$) ($p = 0.0528$). More patients in the insulin glargine group had confirmed nocturnal hypoglycemia of <3.9 mmol/L ($p < 0.05$) and <2.8 mmol/L ($p < 0.05$) than in the rosiglitazone group. The effects on total and LDL cholesterol, and triglyceride levels with insulin glargine contrasted with those of rosiglitazone (-4.4% , -1.4% , and -19.0% vs $+10.1\%$, $+13.1\%$, and $+4.6\%$, respectively; $p < 0.005$). HDL cholesterol was unchanged with insulin glargine but increased with rosiglitazone by 4.4% , $p < 0.05$). Insulin glargine led to less weight gain than rosiglitazone (1.6 ± 0.4 kg vs 3.0 ± 0.4 kg; $p < 0.05$), fewer adverse events (7% vs 29% ; $p < 0.001$), and no peripheral edema (0 vs 12.5%). In conclusion, both triple therapies achieved comparable improvements in HbA1c. Rosiglitazone was associated with less hypoglycemia and more weight gain (Rosenstock et al 2006a).

As shown above, many studies suggest the use of a rosiglitazone/SU combination in different stages of type 2 diabetes. Further studies supporting the concept and efficacy of the fixed dose combination of rosiglitazone with glimepiride are currently under way and their results will soon become publicly available.

Recent findings from the ADOPT trial, a monotherapy outcome study comparing rosiglitazone, metformin, and glyburide over four years (Kahn et al 2006), showed the typical side-effects of each drug class. Gastrointestinal problems were most frequently observed with metformin, sulfonylureas led to hypoglycaemia, and weight gain and edema were most frequently seen with rosiglitazone. In addition, there was a small but significant number of leg and forearm fractures in postmenopausal women with rosiglitazone. As it is known that PPAR γ activation may influence bone metabolism, further research is required to elucidate the impact of these findings on the risk/benefit analysis of the rosiglitazone/glimepiride combination.

Quality of life and patient satisfaction

The fixed combination of glimepiride with rosiglitazone has only been recently approved. Therefore, no report focussing on patient satisfaction with this fixed combination has been published yet. Improved patient satisfaction

with the combination of rosiglitazone and glimepiride given as separate tablets was already reported from the RESULT study (Rosenstock et al 2005; Herman et al 2005). It can, therefore, be expected that the additional reduction of the daily number of tablets to be taken may lead to an even better treatment satisfaction and adherence of the patients to their therapy.

Conclusion

The combination of rosiglitazone with glimepiride has been investigated in multiple trials, some of which especially addressed the benefit of adding a TZD in early stages to low-dose SU therapy vs increasing the SU dose or a head-to-head comparison with the SU/metformin combination. Introducing the synergistic effects of both drug classes at these stages improved overall glycemic control without necessarily increasing the risk for hypoglycemic episodes, and with a safety profile comparable with rosiglitazone mono-therapy. In all studies, more patients on the combination therapy reached the HbA1c treatment target compared with the respective comparator arms. While these trials provide the scientific rationale for combining TZDs with SUs, the introduction of a fixed-dose combination of rosiglitazone and glimepiride may be regarded as a helpful tool to increase patients convenience, since it reduces the number of daily tablets. It may, therefore, support patients' adherence to the essential anti-diabetic therapy. The available pharmacological formulations, allowing for up- or downtitration of the glimepiride doses, may be welcomed by physicians as a means of responding to a potentially increased number of hypoglycemic events without losing metabolic efficacy.

Place in therapy

Based on published investigations, the place for the fixed-dose combination of rosiglitazone and glimepiride may be as a second-line therapeutic approach in patients failing on low- to mid-dose SU mono-therapy and in the triple combination with metformin. In this treatment segment, this fixed combination has to compete with the fixed combination of pioglitazone with glimepiride, which has also been approved recently in the US and Europe.

As mentioned above, the fixed combination of rosiglitazone with glimepiride is available as single tablet formulation containing 4 mg of rosiglitazone with either 1 mg, 2 mg, or 4 mg of glimepiride. It should be given once daily with the first meal of the day and dosage should be

adapted to individual needs in order to obtain the optimal glycemic control with the lowest incidence of adverse events, particularly severe hypoglycemia and heart failure. The maximum recommended dose is 8 mg of rosiglitazone and 4 mg of glimepiride. The recommended starting dose for patients inadequately controlled with SU alone or who had initially responded to rosiglitazone and require a better glycemic control, is 4 mg/1 mg. This starting dose is also recommended in elderly and debilitated patients and in case of renal, hepatic, or adrenal insufficiency. When switching from a combination therapy of rosiglitazone plus glimepiride as separate tablets, the corresponding fixed-dose formulation should be taken and sufficient time should be given to assess adequacy of therapeutic response. If hypoglycemia occurs during the titration, the dose of glimepiride may be reduced (GlaxoSmithKline 2006).

Disclosures

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Abbreviations

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; HOMA, homeostatic model assessment; LDL, low density lipoprotein; SU, sulfonylurea; TZD, thiazolidinedione.

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