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REVIEW

Pioglitazone-Metformin Extended-Release Fixed-Dose Combination for the Treatment of Type 2 Diabetes

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Abstract

Background: Combination oral glucose-lowering drug therapy is often required to maintain glycemic control in patients with type 2 diabetes. Single-tablet fixed-dose combinations of oral glucose-lowering agents provide one means to increase adherence, which may improve metabolic and clinical outcomes. A new fixed-dose combination of pioglitazone and extended-release metformin has recently been approved in the US in dosage strengths of 15 mg/1000 mg and 30 mg/1000 mg.

Aims: To review the clinical pharmacokinetics, efficacy and safety of the fixed-dose combination of pioglitazone and extended-release metformin, and to discuss the rationale behind its development.

Data Sources: English-language articles from PubMed (without date restriction) using key words pioglitazone, metformin, extended-release and fixed-dose combination. Additional sources included published conference abstracts and US prescribing information.

Results: The efficacy and safety/tolerability of pioglitazone and immediate-release metformin as dual therapy have been established in randomized controlled trials. This combination provides durable glycemic control over 2 years and is associated with a low risk of hypoglycemia. Individually, both drugs have evidence for macrovascular benefits. Potential drawbacks include weight gain and edema with pioglitazone and gastrointestinal disturbances with metformin. Published clinical data regarding the specific combination of pioglitazone and extended-release metformin (either as fixed-dose combination or dual therapy) remain scarce. However, bioequivalence between fixed-dose combination and dual therapy has been demonstrated, and studies have confirmed equivalence between extended-release metformin and immediate-release metformin in terms of drug exposure and efficacy/safety. The clinical efficacy/safety profile of the fixed-dose combination of pioglitazone and extended-release metformin can thus be extrapolated from dual therapy studies using immediate-release metformin.

Conclusion: The fixed-dose combination of pioglitazone and extended-release metformin provides a new option when implementing therapy with a well-characterized oral agent combination. As it requires only once-daily dosing with one or two tablets, it may be particularly appropriate for patients in whom adherence is a concern.

Keywords: pioglitazone, metformin, extended-release, fixed-dose combination, type 2 diabetes

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Introduction

Combination oral glucose-lowering drug treatment is often required to maintain glycemic control over the longer term, or as an initial therapy option in patients with higher HbA_{1c} levels.[1–4] The oral glucose-lowering agent metformin is generally regarded as the core component of early glucose-lowering therapy in contemporary treatment guidelines and algorithms, ahead of other potential options, such as sulfonylureas, thiazolidinediones and DPP-4 inhibitors.[1–4] When initial monotherapy with metformin fails, several alternatives for adding a second oral agent may be considered and add-on therapy with pioglitazone represents an effective option that provides superior and more durable glycemic control compared with adding a sulfonylurea (Fig. 1).[1–5]

One potential drawback of combination therapy is the greater treatment complexity associated with using multiple oral glucose-lowering agents, some of which may require multiple daily dosing (up to 3 times per day). This is in addition to numerous other drugs often required to treat the accompanying diseases commonly seen in patients with type 2 diabetes (e.g. hypertension, dyslipidemia, thrombosis and obesity, among others).[6,7] Increasing treatment complexity (in terms of number of oral glucose-lowering agents, number of daily doses or number of other co-medications) can lead to reduced medication adherence, which is associated with poorer glycemic control and an increased risk of adverse clinical outcomes, such as hospitalization.[8–13]

Single-tablet fixed-dose combinations (FDCs) of oral glucose-lowering agents provide an opportunity to decrease treatment complexity by reducing pill burden and thus improving medication adherence.[14] A single-tablet FDC of pioglitazone and immediate-release (IR) metformin has been available in the US (as ACTOplus met®) since August 2005 and in the EU (as Competact®) since July 2006.

Extended-release (XR) formulations of metformin provide an opportunity to reduce treatment complexity further by reducing the metformin dosing requirement from the typical 2–3 times per day to only once per day. An FDC of pioglitazone and metformin XR was approved in the US (as ACTOplus met XR®) in May 2009. This represents the first and (at the time of writing this article) only prescription oral glucose-lowering agent FDC medication that contains an extended-release form of metformin. In the US, it is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with pioglitazone and metformin or who have inadequate glycemic control on pioglitazone monotherapy or metformin monotherapy.[15]

This article describes the characteristics of this new single-tablet FDC of pioglitazone and metformin XR, and discusses the rationale behind its development.

Pioglitazone + Metformin as a Rational Option for Oral Glucose-lowering Combination Therapy

A rational glucose-lowering combination

In theory, combination oral glucose-lowering therapy should be most effective when using agents with complementary mechanisms of action to maximize glucose-lowering potential, especially considering the complex multifactorial pathophysiology of type 2 diabetes.[3,16] Accordingly, many clinical studies show that, when monotherapy starts to fail, addition of a second oral agent from a different drug class is more effective than uptitrating the initial therapy.[17–21] Although pioglitazone and metformin are both considered to be insulin-sensitizing agents, they have partially distinct and complementary glucose-lowering mechanisms of action.[22–27] Metformin's mechanism of action appears to involve AMPK activation (mainly in the liver), whereas pioglitazone activates PPARγ, which regulates multiple genes controlling carbohydrate and lipid metabolism and stimulates mitochondrial biogenesis (*via* upregulation of PPARγ coactivator-1α), as well as having PPARγ-independent effects (including AMPK activation *via* a different pathway to metformin).[26,28]

Furthermore, pioglitazone and metformin have different primary sites of action for their glucose-lowering effects. Metformin acts primarily in the liver, where it inhibits hepatic glucose output and increases glucose uptake, although it may also have some minor effects on glucose uptake in skeletal muscle, intestinal glucose absorption and adipose tissue function, as well as effects on the enteroinsular axis (incretin system).[22,26,29,30] Pioglitazone acts primarily in adipose tissue, where it alters

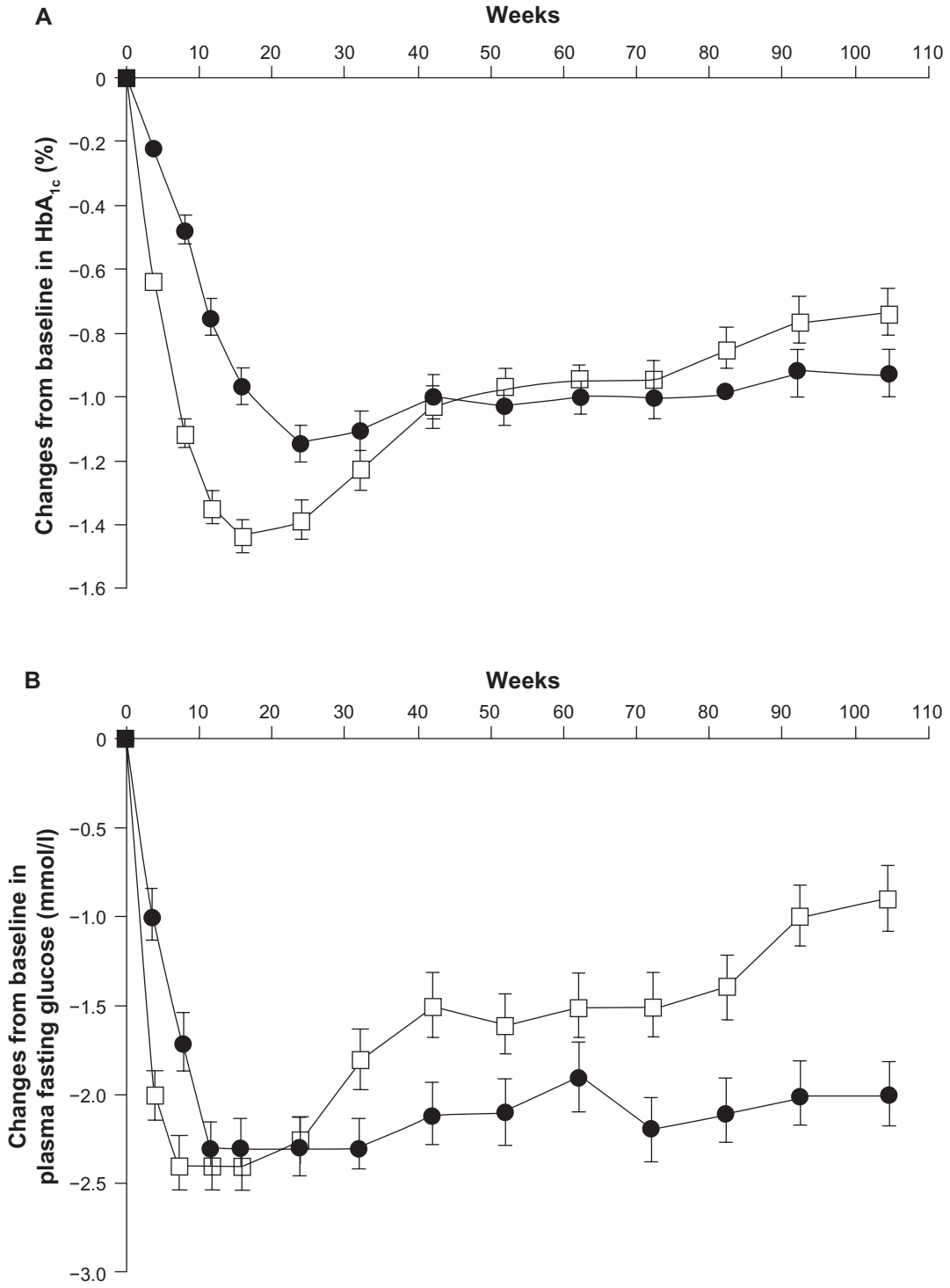

Figure 1. Pioglitazone provides more durable glycemic control compared with gliclazide as add-on therapy to metformin IR (dual therapy).[5] Time course of mean changes ± SEM from baseline to last value (last observation carried forward analysis) for HbA_{1c} **A**) and FPG **B**). Closed circles, pioglitazone add-on to metformin; open squares, gliclazide add-on to metformin. To convert mmol/L to mg/dl divide by 0.0555. This was a 2-year randomized, double-blind, double-dummy, parallel-group study performed in 630 patients with inadequately controlled type 2 diabetes (HbA_{1c} 7.5%–11% inclusive), who were receiving metformin at ≥50% of the maximum recommended dose or at the maximum tolerated dose. Patients received add-on therapy with pioglitazone (15–45 mg/day, n = 317) or gliclazide (80–320 mg/day, n = 313). Reprinted with permission from Charbonnel B, et al. *Diabetologia*. 2005;48:1093–104.

adipokine release, increases non-esterified fatty acid (NEFA) uptake and increases glucose uptake.[25] This leads to secondary effects in the liver (where it decreases hepatic glucose output and stimulates glucose uptake) and skeletal muscle (where it increases glucose uptake).[22,25–27] However, there is good evidence (e.g. based on tissue-specific PPARγ knockout mouse studies) that pioglitazone can also have direct effects in these tissues.[25,27]

The greater effect of pioglitazone on peripheral glucose disposal may explain why pioglitazone has a greater effect on post-load glucose compared with metformin.[23,31] However, there is also evidence that pioglitazone can influence islet β-cells either directly or secondary to effects in adipose tissue.[32] Notably, data from several sources (e.g. based on animal studies of β-cell mass or diabetes prevention in humans) suggest that pioglitazone (and possibly also metformin to a more limited extent) may help to preserve islet β-cell function over the long term, which may be relevant to the durable glycemic control reported with this combination (see below).[32]

Pioglitazone and metformin have complementary effects on lipid profiles.[33–39] Pioglitazone increases HDL-cholesterol, lowers triglycerides and has beneficial effects on LDL particle size distribution, whereas metformin appears principally to reduce total cholesterol and LDL-cholesterol, although the effects are small (Table 1).[33–39] Importantly, the significant improvements in lipid profile with pioglitazone are seen in the setting of add-on therapy to metformin, thus providing an additive benefit, and the effects are sustained over 2 years.[33,35]

Pioglitazone alters circulating levels of a whole range of other adipose-tissue and liver-derived factors with a potential role in inflammation and cardiovascular disease, including adiponectin, C-reactive protein (CRP), matrix metalloproteinase-9 (MMP-9), NEFAs, plasminogen activator inhibitor-1(PAI-1), tumour necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1) and P-selectin (Table 1).[27,40–45] Similarly, metformin also reduces PAI-1 levels, as well as circulating levels of leptin.[46,47] As with lipids, many of these effects of pioglitazone have been shown to occur in the context of add-on therapy to

Table 1. Potential cardioprotective mechanisms for pioglitazone and metformin.

Potential mechanism of cardioprotection	Pioglitazone	Metformin
Reduced hyperglycemia/glucotoxicity	Yes	Yes
Improved insulin sensitivity/reduced hyperinsulinemia	Yes	Yes
Improved lipid profile	↑ HDL-cholesterol, ↓ triglycerides ↓ sdLDL, ↓ NEFAs	↓ Total cholesterol, ↓ LDL-cholesterol
Altered adipokine/cytokine levels	↑ adiponectin, ↓ CRP, ↓ MMP-9, ↓ PAI-1, ↓ TNFα, ↓ MCP-1, ↓ P-selectin	↓ PAI-1, ↓ leptin
Direct effects in the vasculature	Endothelial cells (↓ myocyte adhesion, ↓ endothelial inflammation, ↓ endothelial dysfunction), VSMCs (↓ proliferation, ↓ migration, ↓ apoptosis), macrophages (↓ inflammation, ↓ cholesteryl ester accumulation)	Endothelial cells (↓ myocyte adhesion; ↓ apoptosis); macrophages (↓ lipid uptake)
Reduced blood pressure	Yes	No
Improved microvascular blood flow	Yes	Yes
Fat redistribution	↓ visceral, ↓ liver, ↓ intramyocellular	↓ visceral, ↓ intramyocellular
Improved cardiac function and recovery from ischemic injury	Yes	Yes

Home & Pacini;[27] Davidson et al;[34] Betteridge;[35] Buse et al;[36] Chiquette et al;[37] Wulffelé et al;[38] Goldberg et al;[39] Pfützner et al;[40] Derosa et al;[41] Forst et al;[42] Karagiannis et al;[43] Miyazaki and DeFronzo;[44] Erdmann and Wilcox;[45] Scarpello and Howlett;[46] Sharma et al;[47] Sarafidis and Nilsson;[48] Duan et al;[49] Forst et al;[50] van de Meer et al;[51] Miyazaki et al;[52] Teranishi et al;[53] Gupta et al.[54]

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; NEFA, non-esterified fatty acid; PAI-1, plasminogen activator inhibitor-1; sdLDL, small dense LDL; TNFα, tumour necrosis factor-α; VSMC, vascular smooth muscle cell.

metformin. Pioglitazone, but not metformin, also has well documented beneficial effects on blood pressure.[38,48]

Both pioglitazone and (to a lesser extent) metformin also have direct potentially beneficial effects on key cells types in the vasculature with a role in the development of vascular disorders (vascular smooth muscle cells [VSMCs], macrophages and endothelial cells).[45,46,49] Both pioglitazone and metformin have also been shown to improve microvascular blood flow.[46,50] Some evidence also suggests that pioglitazone can improve cardiac function and myocardial glucose uptake.[51]

Pioglitazone (and possibly metformin in some organs) can also reduce ectopic fat accumulation. Both pioglitazone and metformin have been shown to cause a shift of fat distribution from high-risk visceral to lower-risk subcutaneous adipose depots.[46,52] Pioglitazone, but not metformin, significantly decreases liver fat.[51,53,54] Excess liver fat is associated with insulin resistance, risk of coronary artery disease and early atherosclerosis.[27,55] Both metformin and pioglitazone also appear to decrease intracellular lipid content in skeletal muscle.[52]

An established effective glucose-lowering combination

Accordingly, randomized clinical trials (RCTs) have shown that pioglitazone and metformin offer an effective oral glucose-lowering agent combination, especially when pioglitazone is used as add-on therapy in patients poorly controlled on stable metformin monotherapy (Table 2).[5,56–65] In a 16-week placebo-controlled study in 328 patients failing on metformin monotherapy ($HbA_{1c} \geq 8\%$; mean 9.8%), add-on therapy with pioglitazone significantly improved HbA_{1c} (−0.83% versus placebo) and fasting plasma glucose (FPG) levels (−38 mg/dL versus placebo).[58] It is worth noting that, based on a *post-hoc* analysis from this study, the HbA_{1c}-lowering effect of pioglitazone as an add-on to metformin may have been underestimated, as it was attenuated in those patients who were on metformin/sulfonylurea combination therapy prior to enrolment and discontinued the sulfonylurea before staring the trial.[66] Some patients (83 from the pioglitazone group and 71 from the placebo group) elected to enter an open-label extension study on pioglitazone-metformin therapy.[58] After 72 weeks of open-label therapy, these patients had mean changes from baseline (start of the original 16-week double-blind study) of −1.36% in HbA_{1c} and −63.0 mg/dL in FPG. A recent 28-week placebo-controlled study looked at pioglitazone add-on therapy in 169 Japanese patients suboptimally controlled on metformin monotherapy ($HbA_{1c} \geq 6.5\%$; mean 7.6%).[59] Patients receiving pioglitazone achieved significantly greater reductions in HbA_{1c} and FPG compared with placebo and significantly more patients achieved $HbA_{1c} < 6.5\%$ (Table 2).

Several studies have also shown that metformin/pioglitazone combination therapy is an effective alternative to metformin/sulfonylurea combination therapy and is more effective over the long term.[5,60,61] A 2-year double-blind study compared addition of pioglitazone or gliclazide in 640 patients failing on metformin monotherapy (7.5%–11.0%, inclusive, mean 8.6%) at ≥50% of the recommended dose or the maximum tolerated dose.[5] In an initial 1-year analysis, glycemic control improved in both groups and there were no significant differences between pioglitazone and gliclazide in terms of reduction in HbA_{1c} (−0.99% versus 1.01%, respectively) or FPG (−34.2 mg/dL versus −30.6 mg/dL, respectively) and the two groups appeared to be equally effective.[60] However, it was readily apparent that, whereas the onset of effect with pioglitazone was slow and sustained, the effect of add-on gliclazide therapy declined markedly over time after peaking rapidly at 16 weeks. Thus, in the 2-year analysis, further deterioration in the gliclazide group, alongside a continued sustained effect in the pioglitazone group, caused a separation of glycemic control between the two groups.[5] The mean reduction from baseline in HbA_{1c} was 0.89% for pioglitazone and 0.77% for gliclazide addition to metformin (although the difference failed to achieve statistical significance; $P = 0.20$) and there was a statistically significant between-group difference for the change in mean FPG (−32.4 mg/dL versus −19.8 mg/dL, respectively; $P < 0.001$) (Fig. 1). This study, therefore, indicates the durability of glycemic control with the metformin plus pioglitazone versus the metformin plus sulfonylurea combination. A subsequent 2-year analysis in the subset of patients who underwent 3-h

Table 2. Key metabolic outcomes in RCTs of pioglitazone-metformin combination therapy.

Study	N	Duration (weeks)	Baseline HbA_{1c}	Intervention	Change in HbA_{1c}	Change in FPG
Pioglitazone vs. placebo as add-on to metformin						
Einhorn et al[58]	328	16	~9.8%	Pioglitazone 30 mg/day + metformin Placebo + metformin (Metformin dose NA; 60% <2000 mg/day)	Significantly greater reduction in the pioglitazone arm ($P \leq 0.05$): Pioglitazone + metformin: ~–0.63% Placebo + metformin: ~+0.2%	Significantly greater reduction in the pioglitazone arm ($P \leq 0.05$): Pioglitazone + metformin: –42.2 mg/dL Placebo + metformin: –4.5 mg/dL
Kaku[59]	169	28	~7.6%	Pioglitazone 30 mg/day[a] + metformin Placebo + metformin (Metformin dose 500 or 750 mg/day)	Significantly greater reduction in the pioglitazone arm ($P < 0.0001$): Pioglitazone + metformin: –0.67% Placebo + metformin: +0.25%	Significantly greater reduction in the pioglitazone arm ($P < 0.0001$): Pioglitazone + metformin: –20.5 mg/dL Placebo + metformin: +1.9 mg/dL
Pioglitazone vs. sulfonylurea as add-on to metformin						
Charbonnel et al;[5] Matthews et al[60]	630	104	~8.6%	Pioglitazone (up to 45 mg/day) + metformin Gliclazide (up to 320 mg/day) + metformin (Metformin dose ≤2550 mg/day [mean: 2074 mg/day])	Comparable change from baseline: Pioglitazone + metformin: –0.89% Gliclazide + metformin: –0.77%	Significantly greater reductions with pioglitazone ($P < 0.001$): Pioglitazone + metformin: –32.4 mg/dL Gliclazide + metformin: –19.8 mg/dL
Umpierrez et al[61]	203	26	~8.3%	Pioglitazone up to 45 mg/day + metformin Glimepiride up to 8 mg/day + metformin (Metformin dose: IR 1000–2500 mg/day or XR 500–2000 mg/day [overall mean: ~2000 mg/day])	Comparable change from baseline: Pioglitazone + metformin: –1.3% Glimepiride + metformin: –1.2%	Comparable change from baseline: Pioglitazone + metformin: –39.7 mg/dL Glimepiride + metformin: –34.1 mg/dL
Pioglitazone vs. rosiglitazone as add-on to metformin						
Derosa et al[62]	96	52	~8.2%	Pioglitazone 15 mg/day + metformin Rosiglitazone 4 mg/day + metformin (Metformin dose 1500–3000 mg/day)	Comparable change from baseline: Pioglitazone + metformin: ~–1.4% Rosiglitazone + metformin: ~–1.4%	Comparable change from baseline: Pioglitazone + metformin: ~–21 mg/dL Rosiglitazone + metformin: ~–22 mg/dL

(*Continued*)

Table 2. (*Continued*)

Study	N	Duration (weeks)	Baseline HbA_{1c}	Intervention	Change in HbA_{1c}	Change in FPG
Pioglitazone vs. vildagliptin as add-on to metformin						
Bolli et al[63]	576	52	~8.4%	Pioglitazone 30 mg/day + metformin Vildagliptin 50 mg BID metformin (Metformin dose ≥1500 mg/day [mean: 2000 mg/day])	Comparable change from baseline: Pioglitazone + metformin: –0.6% Vidlagliptin + metformin: −0.6%	Comparable change from baseline: Pioglitazone + metformin: –29 mg/dL Vildagliptin + metformin: –18 mg/dL
Pioglitazone vs. placebo as add-on to metformin XR						
Kupfer et al[64]	315	16	NA	Pioglitazone 30 mg/day + Metformin XR 1000 mg/day Placebo + Metformin XR 1000 mg/day	Significantly greater reduction in the pioglitazone arm ($P \leq 0.0001$): Pioglitazone + metformin XR: –0.81% Placebo + metformin XR: +0.21%	Significantly greater reduction in the pioglitazone arm ($P \leq 0.0001$): Pioglitazone + metformin: –30.6 mg/dL Placebo + metformin: +9.9 mg/dL
Pioglitazone-metformin IR FDC vs. pioglitazone monotherapy vs. metformin IR monotherapy (all as first-line therapy)						
Perez et al[65]	600	24	~8.8%	Pioglitazone 15 mg/ metformin 850 mg BID FDC Pioglitazone 15 mg BID Metformin 850 mg BID	Significantly greater reduction in the FDC arm vs. both monotherapy arms ($P \leq 0.0001$): Pioglitazone-metformin FDC: –1.83% Pioglitazone: –0.96% Metformin: –0.99%	Significantly greater reduction in the FDC arm vs. both monotherapy arms ($P \leq 0.01$): Pioglitazone-metformin FDC: –39.3 mg/dL Pioglitazone: –22.2 mg/dL Metformin: –24.8 mg/dL

[a]15 mg/day for 12 weeks, then 30 mg/day for 16 weeks.
Abbreviations: FDC, fixed-dose combination; FPG, fasting plasma glucose; IR, immediate-release; NA, not available; XR, extended-release.

oral glucose tolerance testing in this study showed that pioglitazone addition to metformin achieved reductions in post-load glucose excursions with concomitant reductions in post-load insulin levels, whereas add-on therapy with gliclazide resulted in increases in post-load glucose excursions, despite increases in post-load insulin concentrations.[31]

A 26-week open-label study compared the addition of pioglitazone or glimepiride in 203 patients poorly controlled on stable doses of metformin IR or XR monotherapy (HbA_{1c} 7.5%–10.0%, inclusive, mean 8.3%).[61] Both treatments achieved similar and significant mean decreases from baseline to endpoint (Week 26) in HbA_{1c} and FPG.

Due to the progressive nature of type 2 diabetes, durability of glycemic control is an important consideration for oral glucose-lowering therapy.[16] As monotherapy, metformin and pioglitazone each provide

more stable long-term glycemic control compared with sulfonylureas,[67,68] predicting the durable control seen over 2 years with their combination (Fig. 1).[5] In a study based on the design of the UK prospective Diabetes Study (UKPDS), patients allocated to open-label combination therapy with metformin plus pioglitazone experienced a slower deterioration in glycemic control compared with metformin in combination with either gliclazide or repaglinide for up to 3 years.[69]

Two other RCTs looking at pioglitazone add-on therapy in metformin-treated patient are also worth mentioning, one using rosiglitazone as the comparator and another using the DPP-4 inhibitor vildagliptin.[62,63] In both studies, add-on therapy with pioglitazone or comparator provided similar significant reductions from baseline for HbA_{1c} and FPG after 1 year (Table 2). Some further studies relating to pioglitazone/metformin XR combination dual therapy (as add-on therapy in patients failing metformin XR) and first-line therapy with a FDC of pioglitazone-metformin IR are discussed below (Table 2).[64,65]

A well-characterized, well-tolerated combination

One of the potential benefits of combination oral glucose-lowering therapy compared with uptitrated monotherapy is the opportunity to improve glycemic control without worsening tolerability or even to improve tolerability through dose reduction.[14] Pioglitazone and metformin have well-characterized distinct tolerability profiles, thus reducing the potential for additive effects.[46,56,70] The most common events are generally gastrointestinal disturbances with metformin and edema with pioglitazone.[46,56,70] Important rare events include lactic acidosis with metformin (although the risk appears to be minimal if contraindications are taken into account) and fractures (in post-menopausal women) and heart failure (that does not appear to be associated with adverse outcomes) with pioglitazone.[71–73]

Adverse event rates with the combination are generally predictable and do not occur with any greater frequency than those seen in monotherapy studies with either agent at approximately similar doses.[70] Similarly, addition of pioglitazone to metformin does not appear to have much impact on the adverse event profile compared with addition of placebo (apart from a small increase in the rate of edema), even without reducing the dose of metformin.[58,59] Studies also show that addition of pioglitazone to metformin is associated with a similar overall incidence of adverse events compared with addition of a sulfonylurea in metformin-treated patients, although predictably, there is a greater frequency of hypoglycemia in sulfonylurea-treated patients and a greater frequency of edema in pioglitazone-treated patients.[5,60,61,70] Notably, pioglitazone and metformin are two oral glucose-lowering agents with a low propensity to induce hypoglycemia and this favorable characteristic persists when the two drugs are used in combination (adding pioglitazone to metformin does not increase the rate of hypoglycemia compared with metformin alone).[58,70] Across the two placebo-controlled studies described above, only three patients experienced a hypoglycemic event (two in the pioglitazone/metformin groups and one in the placebo/metformin groups).[58,59] In the study by Charbonnel and colleagues, only 2.2% of patients on pioglitazone/metformin combination therapy experienced symptoms of hypoglycemia over 2 years compared with 11.5% of patients on gliclazide/metformin combination therapy.[5] The difference was even more marked in the study by Umpierrez and co-workers, where hypoglycemia was reported for only 0.9% of patients on pioglitazone/metformin combination therapy over 26 weeks compared with 33% on glimepiride/metformin combination therapy.[61]

Weight gain may also be an issue with pioglitazone and the anorectic effects of metformin provide an opportunity to minimize this effect with combination therapy.[70] The amount of weight gain experienced in RCTs when pioglitazone is added to existing metformin therapy is typically in the region of 1–2 kg, which is considerably less than would be expected based on the large improvements in glycemic control.[74] Despite weight gain of 2.6 kg gain with addition of pioglitazone to metformin in a 1-year RCT, this combination provided similar improvements in efficacy to addition of vildagliptin to metformin, which produced a weight gain of only 0.2 kg.[63] However, in one RCT, the addition of pioglitazone to

metformin was not associated with any weight gain over 1 year.[62]

Potential cardiovascular benefits

Pioglitazone and metformin represent the only two individual oral glucose-lowering agents with robust evidence for a reduction in macrovascular risk, thus providing the potential for improved cardiovascular protection when used in combination. In the supplementary study of overweight patients with type 2 diabetes in the UKPDS, those allocated to initial intensive therapy with metformin experienced a significant reduction in the risk of all-cause mortality (relative risk reduction [RRR] = 36%) or myocardial infarction (RRR = 39%) compared with less intensive therapy (principally lifestyle intervention) over a median of 10.7 years.[75] These benefits persisted after 10 years of post-trial follow-up, despite considerable therapeutic overlap between the groups after the end of randomized therapy.[76] Metformin also significantly reduced the risk of all-cause mortality or stroke compared with insulin/sulfonylureas in the initial study.[75]

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), pioglitazone did not reduce the risk of the primary endpoint (a complex composite of coronary, cerebrovascular and peripheral macrovascular events) relative to placebo over approximately 3 years in high-risk patients with type 2 diabetes and established macrovascular disease (hazard ratio [HR] = 0.90, 95% CI [0.80, 1.02]; $P = 0.095$).[77,78] However, pioglitazone did reduce the risk of macrovascular events based on several other more conventional composite endpoints, including the main secondary endpoint (all-cause mortality, myocardial infarction [MI], or stroke; HR = 0.84, 95% CI [0.72, 0.98]; $P = 0.027$) and the composites of cardiovascular (CV) death, MI or stroke (HR = 0.82, 95% CI [0.70, 0.97]; $P = 0.020$), CV death, MI, stroke or acute coronary syndrome (HR = 0.80, 95% CI [0.69, 0.94]; $P = 0.005$), and fatal/non-fatal MI (HR = 0.77, 95% CI [0.60, 1.00]; $P = 0.046$).[77–79] Pioglitazone appeared to be particularly effective at reducing the risk of recurrent MI (HR = 0.72, 95% CI [0.52, 0.99]; $P = 0.045$) or recurrent stroke (HR = 0.53, 95% CI [0.34, 0.85]; $P = 0.009$).[80,81]

Furthermore, pioglitazone has been shown to reduce the progression of coronary atherosclerosis (measured directly using intravascular ultrasound [IVUS] with glimepiride as comparator) in the PERISCOPE study.[82] Pioglitazone also slowed the progression of carotid atherosclerosis (based on measurement of carotid intima-media thickness [CIMT]) compared with glimepiride in patients with type 2 diabetes in the CHICAGO study.[83] This latter effect appears to be linked to the ability of pioglitazone to increase HDL cholesterol.[34]

The effects of pioglitazone—metformin combination therapy on macrovascular outcomes have not been studied in any detail in either observational studies or RCTs. However, as noted above, in addition to their effects on glucose homeostasis and insulin sensitivity, pioglitazone and metformin also have distinct and complementary favorable effects on lipid homeostasis, inflammatory mediators and other markers with potential involvement in the development of cardiovascular disease, suggesting the potential for additive benefits with regards to CV outcomes (Table 1).

Optimizing Pioglitazone-metformin Therapy with a Fixed-dose Combination

The evidence presented above suggests that combination therapy with metformin and pioglitazone represents an effective, well-tolerated option for improving glycemic control, with a low risk of hypoglycemia and the potential for improved macrovascular outcomes. However, one potential drawback with traditional dual combination therapy is the ensuing increase in treatment complexity. Many retrospective and prospective studies suggest that increasing treatment complexity is associated with poorer adherence, which is in turn associated with poorer metabolic control (i.e. higher HbA_{1c} levels) and worse clinical outcomes, such as all-cause hospitalization and mortality.[8–13] It is not surprising, therefore, that poor adherence can be associated with increased healthcare costs in patients with type 2 diabetes.[84,85] Thus, failure to address poor adherence as a root cause of poor glycemic control may limit the benefits achievable when treatment is intensified. Poor adherence can also have an adverse influence on physician prescribing behavior and actually prevent appropriate treatment intensification by contributing to clinical inertia.[86]

Adherence has been shown to worsen specifically with increasing number of daily doses or increasing number of co-medications.[8–10] Notably, dual therapy with two separate oral glucose-lowering agents is associated with poorer adherence compared with either monotherapy alone.[9] It is therefore perhaps unsurprising that single-tablet FDCs of oral glucose-lowering agents have been shown to improve adherence significantly compared to dual therapy with the constituent oral glucose-lowering agents.[87] These FDCs also have the added advantage of being significantly cheaper than the sum of the individual constituent drugs.[87]

An FDC of pioglitazone and metformin IR has been approved for several years and provides a reduction in treatment complexity compared with pioglitazone/metformin dual therapy by decreasing the total number of daily tablets. It is available in the US in dosage strengths of 15 mg/500 mg or 15 mg/850 mg pioglitazone-metformin IR (in the EU, only 15 mg/850 mg is available) and the maximum recommended dose is 45 mg/2550 mg per day.[15] The dosing schedule is constrained by the pharmacokinetic characteristics of the metformin IR component—while pioglitazone needs to be taken only once per day without regard to meals, metformin IR (and hence the pioglitazone/metformin IR FDC) typically needs to be taken 2–3 times per day with meals.

Extended-release (XR) formulations of metformin provide an opportunity to reduce treatment complexity further. A single evening meal-time dose of metformin XR can provide equivalent overall drug exposure to that achieved with multiple daily doses of metformin IR.[88,89] Clinical studies demonstrate that once-daily metformin XR formulations show similar glucose-lowering efficacy to twice/thrice-daily IR formulations at equivalent total daily doses.[88–92] Furthermore, some evidence suggests that metformin XR may have better gastrointestinal tolerability than metformin IR.[93]

An FDC of pioglitazone-metformin XR thus provides an opportunity to lower the number of daily tablets further and to reduce the dosing schedule to just a single dose to be given with the evening meal, thus decreasing regimen complexity without compromising glucose-lowering efficacy. Pioglitazone-metformin XR has recently been approved in the US and represents the first available FDC to contain an XR formulation of metformin.[15]

Pioglitazone-metformin XR—Physicochemical Characteristics

The pioglitazone-metformin XR FDC tablet consists of an extended-release metformin core coated tablet with an immediate-release pioglitazone layer.[15] The metformin core tablet is an XR formulation using the patented single composition osmotic technology (SCOT™; identical to that used with Fortamet XR metformin).[15,88] The osmotically-active core formulation is surrounded by a semipermeable membrane that is coated with the pioglitazone drug layer.[15] Two laser-drilled exit ports are incorporated into the membrane—one on either side of the tablet.[15] The membrane is permeable to water, but not to higher molecular weight components of biological fluids.[15]

Upon ingestion, the pioglitazone layer is dissolved and water is then taken up through the membrane, which in turn dissolves the metformin and excipients in the core formulation.[15] The dissolved metformin and excipients exit through the laser-drilled ports in the membrane.[15] The rate of drug delivery is constant as long as undissolved metformin is present in the core and is dependent upon the maintenance of a constant osmotic gradient across the membrane.[15] Following the dissolution of the core materials, the rate of drug delivery slowly decreases until the osmotic gradient across the membrane falls to zero, at which time delivery ceases.[15] The membrane coating remains intact during transit through the gastrointestinal tract and is excreted in the feces.[15]

At present, the FDC is available in the US in dosage strengths of 15 mg/1000 mg and 30 mg/1000 mg pioglitazone-metformin XR.[15] This allows permutations of 15, 30 or 45 mg pioglitazone or 2000 mg metformin XR (the maximum recommended doses) to be administered as a single evening meal-time dose using one or two tablets (the only permutation that is not possible is 15 mg/2000 mg).

Pioglitazone-metformin XR—Clinical Characteristics

Pharmacokinetic profile

As expected, metformin XR tablets such as Fortamet exhibit slower and more prolonged pharmacokinetics compared with metformin IR formulations.[88] When Fortamet is administered at 2000 mg QD, it has a t_{max} of ~6 hours and a C_{max} of 2849 ng/mL whereas

metformin IR administered at 1000 mg BID has a t_{max} of ~3 hours and a C_{max} of 1820 ng/mL.[88] Importantly, however, at these equivalent doses, total daily drug exposure is comparable between the two formulations, with $AUC_{0-24\ h}$ values of 26,811 ng · h/mL for Fortamet and 27,371 ng · h/mL for metformin IR and, in this and several other studies, geometric mean ratios for AUC are close to unity.[88] Furthermore, Fortamet provides a predictable and consistent dose-associated increase in metformin exposure within the dose range 1000–2500 mg.[94]

In bioequivalence studies of pioglitazone-metformin XR 15 mg/1000 mg and 30 mg/1000 mg, the AUC and C_{max} of both the pioglitazone and the metformin XR components following a single dose of the FDC tablet were equivalent to pioglitazone 15 mg and 30 mg concomitantly administered with metformin XR 1000 mg (Fortamet) tablets as dual therapy under fed conditions in healthy subjects.[15] For the 15 mg/1000 mg dose, mean (±SD) total pioglitazone exposure ($AUC_{(0-\infty)}$) was 5113 ± 1598 ng · h/mL with FDC therapy and 5979 ± 1726 ng · h/mL with dual therapy, whereas total metformin exposure was 14454 ± 3579 and 14787 ± 3313 ng · h/mL, respectively.[15] Similarly, for the 30 mg/1000 mg dose, total pioglitazone exposure was 8242 ± 2587 ng · h/mL with FDC therapy and 9177 ± 2200 ng · h/mL with dual therapy, whereas total metformin exposure was 12705 ± 3577 and 12796 ± 3882 ng · h/mL, respectively.[15] Pioglitazone-metformin XR 30 mg/1000 mg with food resulted in no change in total exposure of pioglitazone, although a decrease in C_{max} by approximately 18% was observed.[15] For the metformin XR component, there was an increase in C_{max} by approximately 98% and AUC exposure by approximately 85% when administered with food. These levels are comparable to exposures obtained with metformin XR when administered with food.[15] Time to C_{max} (t_{max}) was prolonged by approximately 3 and 2 hours for pioglitazone and metformin XR respectively, under fed conditions.[15]

Therapeutic profile

To date, no clinical studies have assessed the efficacy of the pioglitazone-metformin XR FDC tablet specifically. However, the efficacy and tolerability of pioglitazone and metformin IR dual therapy have been well established in randomized controlled trials (see above). Such studies can be used to define the efficacy-tolerability profile of pioglitazone-metformin XR based on bioequivalence with pioglitazone plus metformin XR dual therapy and studies confirming equivalence between metformin XR and metformin IR in terms of drug exposure and clinical efficacy/safety.[95] The starting doses of pioglitazone-metformin XR FDC are, therefore, based on the patient's current regimen of pioglitazone and/or metformin and the usual starting doses of these two drugs (15–30 mg/day pioglitazone and 850–1000 mg/day metformin).[15] The total daily doses of pioglitazone-metformin XR FDC should not exceed the maximum recommended total daily doses of pioglitazone (45 mg) or metformin XR (2000 mg; note that this is slightly lower that the recommended maximum daily dose of 2550 mg for metformin IR).[15] Any precautions or contraindications have been extrapolated from the respective prescribing information for pioglitazone or metformin IR (or metformin XR).[15,95]

Preliminary results have been presented from a 16-week, placebo-controlled, double-blind RCT looking at dual therapy with pioglitazone plus metformin XR (Fortamet).[64] The addition of pioglitazone 30 mg QD to metformin XR 1000 mg QD was associated with a significant reduction in HbA_{1c} compared with the addition of placebo to metformin XR (–0.81% versus +0.21%; difference = –1.02%, 95% CI [–1.29, –0.74]; $P < 0.0001$) and significantly more patients (70% versus 25%; $P < 0.0001$) were considered to be responders ($HbA_{1c} \leq 7\%$ or $\geq 0.6\%$ decrease) (Table 2).[64] In addition, there were similar significant improvements in FPG concentrations and response rates (based on ≥30 mg/dL decrease).[64] The pioglitazone/metformin XR dual therapy combination was well tolerated and over 95% of patients in this treatment group completed the study.[64]

In addition, a recent 24-week study in 600 treatment-naïve patients with type 2 diabetes poorly controlled on lifestyle intervention (HbA_{1c} 7.5%–10%, inclusive; mean ~8.8%) showed that the pioglitazone-metformin IR FDC tablet (15/850 mg BID) provided significantly greater decreases in HbA_{1c} and FPG compared with metformin 850 mg BID or pioglitazone 15 mg BID monotherapy (Table 2).[65] The HbA_{1c} reduction at final visit was 1.83% for pioglitazone-metformin FDC compared with 0.96% and 0.99% for pioglitazone and metformin monotherapy, respectively, thus demonstrating additive effects for the FDC formulation relative to pioglitazone

and metformin alone.[65] More patients in the FDC group reached target $HbA_{1c} \leq 7.0\%$ compared with pioglitazone or metformin monotherapy (64% versus 46% and 39%, respectively).[65] There were also significant improvements in insulin sensitivity and CRP with the FDC formulation that were attributable mainly to the pioglitazone component.[65] The safety/tolerability profile of the FDC was predictable. The overall incidences of treatment-emergent adverse events were similar across the three study groups, with 50.7% for pioglitazone-metformin FDC, 52.1% for pioglitazone monotherapy and 53.1% for metformin monotherapy, and only 1%–1.5% experienced serious events in each group.[65] There were, however, predictable differences in the type of events seen. The incidence of peripheral edema in the FDC, pioglitazone monotherapy and metformin monotherapy groups was 3.0%, 4.2% and 1.4%, respectively, whereas the incidence of gastrointestinal events was 17.9%, 10.5% and 25.8%, respectively.[65] Weight change from baseline was +1.64 kg with pioglitazone monotherapy, −1.28 kg with metformin monotherapy and, as predicted, there was less weight gain with FDC therapy (+0.69 kg).[65] Rates of hypoglycemia were low (1.0%, 0.5% and 1.4% for pioglitazone/metformin FDC, pioglitazone and metformin, respectively), and the slightly higher rate with FDC therapy is consistent with better glycemic control.[65] Thus, pioglitazone-metformin IR FDC therapy provided better efficacy (as expected) and also slightly better tolerability compared with the constituent monotherapies at the same doses. These two factors likely contributed to the lower dropout rate seen with in the FDC group (21.9%) compared with the pioglitazone (33.9%) and metformin (32.4%) monotherapy groups.[65]

A recent observational study, using results obtained from a non-selected patient population (n = 4866) in Germany under daily routine conditions looked at metabolic changes 16 weeks after switching patients from metformin monotherapy to the pioglitazone-metformin IR FDC.[96] There were significant improvements in multiple metabolic parameters, including HbA_{1c}, FBG, total cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, CRP, alkaline phosphatase and systolic and diastolic BP. Of particular note, there was no increase in BMI after switching to pioglitazone-metformin IR FDC therapy. The results were similar, irrespective of whether patients received one or two FDC tablets per day.[96]

Conclusions

Optimal oral glucose-lowering drug combination therapy may not always be achievable due to the adverse impact of poor medication adherence. Although the factors affecting medication-taking behavior in an individual may be complex, the advent of FDC formulations provides one means to help increase adherence and thus improve metabolic and clinical outcomes.

Combination oral glucose-lowering drug therapy with pioglitazone and metformin is an established effective treatment option, especially in patients failing on initial metformin monotherapy, and brings together two agents with recognized macrovascular benefits. The good tolerability profile of this combination (especially the low risk of hypoglycemia) provides another potential contributor to better adherence. The new once-daily FDC of pioglitazone and XR metformin provides a new option when initiating this strategy, for consideration alongside dual therapy and the FDC of pioglitazone and metformin IR.

As the only available FDC that includes an XR metformin formulation, pioglitazone-metformin XR currently represents an efficient and convenient way to implement combination treatment based on what is generally accepted as the cornerstone of early glucose-lowering therapy (i.e. metformin). Based on current recommendations for the use of metformin as the first-line treatment of choice (in the absence of contraindications), pioglitazone-metformin XR is likely to be used most frequently as the second stage of therapy when metformin monotherapy starts to fail. Similarly, it may also be used as the second stage in instances where pioglitazone has been used as the first-line treatment. However, some guidelines advocate the use of combination therapy (including the combination of metformin and a thiazolidinedione) as first-line treatment in patients with higher HbA_{1c} levels,[1,4] and data with the pioglitazone-metformin IR FDC formulation suggest that it may be useful in this setting.[65]

The decision as to which of the three methods of implementing pioglitazone/metformin combination therapy (dual therapy, IR FDC therapy or XR FDC therapy) is most appropriate will need to be made on an individual patient basis. The greater convenience provided by the FDC formulations

(especially pioglitazone-metformin XR) may make them a particularly appropriate choice for patients where poor adherence is a concern, but this will need to be balanced against a possible decrease in dosing flexibility. Certainly, there may be patients where individual titration of dual therapy is the preferred option, at least in the first instance. Other factors, such as cost, may also need to be taken into consideration.

In conclusion, the use of pioglitazone-metformin combination therapy provides an effective and well-tolerated strategy for improving glycemic control and a potential means to improve cardiovascular outcomes in patients with type 2 diabetes. The FDC pioglitazone-metformin XR represents the latest step in the evolution of this strategy.

Disclosures

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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