

Patient considerations and clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes

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Introduction: Targeting glycated hemoglobin (HbA_{1c}) levels below 7.0% is considered a primary goal of diabetes care, given its importance in obtaining a sustained reduction in microvascular, and possibly macrovascular complications.

Aim: The aim of this review was to evaluate the clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes.

Evidence review: The combination of saxagliptin/metformin was well tolerated and produced sustained glycemic control for up to 76 weeks, with greater improvements in glycemic parameters compared with either drug alone. The saxagliptin/metformin combination also proved its non-inferiority compared with either sulfonylurea/metformin or sitagliptin/metformin combinations.

Place in therapy: Clinical practice recommends lifestyle interventions together with starting metformin at the time that the type 2 diabetes mellitus is diagnosed. Once metformin fails to maintain glycemic control, the addition of DPP-4 inhibitors should be the logical choice because of their effects on HbA_{1c} compared to the addition of a sulfonylurea or glitazone, and because of their positive effects on beta cell function and their neutral effects on body weight. Furthermore, DPP-4 inhibitors prevent the risk of hypoglycemia posed by sulfonylureas.

Keywords: DPP-4 inhibitors, saxagliptin, glycemic control, insulin sensitivity, HOMA index

Introduction

Targeting glycated hemoglobin (HbA_{1c}) levels below 7.0% is considered a primary goal of diabetes care, given its importance in obtaining a sustained reduction in microvascular, and possibly macrovascular complications.¹ However, maintaining adequate metabolic control is still a challenge in many patients with type 2 diabetes mellitus (T2DM).² Current guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) recommend early initiation of combination therapy with oral antidiabetic drugs in patients with HbA_{1c} > 8.5% and 7.6%–9.0%, respectively.^{1,3} In particular metformin is recommended (unless specifically contraindicated) as a first-line agent for monotherapy and combination therapy for patients with T2DM. This recommendation is based primarily on metformin's glucose-lowering effects, absence of weight gain, generally low level of side effects, and relatively low cost.^{1,3}

While monotherapy with oral antidiabetic drugs may be effective in improving glycemic control in the short term, dose adjustments or combination therapy are often

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required for long-term control because of the progressive loss of β -cell function and increase in insulin resistance.⁴ In this regard, recent breakthroughs in the understanding of incretin-based therapies have provided additional options for the treatment of T2DM. Incretins are gastrointestinal hormones released during nutrient absorption to increase insulin secretion. The two gut peptides accounting for most of the incretin effect are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). In response to a meal, GLP-1 and GIP are released and, in turn, stimulate insulin (both in a glucose-dependent manner), delay gastric emptying, and increase satiety.^{5,6} Furthermore, GLP-1 acts on alpha cells and inhibits the secretion of glucagons.⁷ Within some minutes of release from their intestinal sites, GIP and GLP-1 undergo rapid metabolism (proteolytic cleavage) to inactive metabolites by the enzyme dipeptidyl peptidase-4 (DPP-4). In T2DM, GLP-1 concentrations are reduced in response to a meal, whereas GIP concentrations are normal or increased. This observation suggests resistance to the action of GIP, making GLP-1 the favored potential therapeutic target.⁸

Because GLP-1 is rapidly degraded by DPP-4,⁹ a new class of compounds have been developed: DPP-4 inhibitors, that delay endogenous degradation of GLP-1 and GIP. Inhibition of the proteolytic DPP-4 enzyme results in a two- to three-fold increase in circulating levels of GLP-1 and GIP, suppressing glucagon secretion in the post-prandial state, stimulating glucose dependent insulin secretion from pancreatic β -cells,¹⁰⁻¹² and decreasing hepatic glucose production in the fasting state, thereby reducing both fasting plasma glucose (FPG) and post-prandial glucose (PPG).^{4,13} The first DPP-4 inhibitor released for use in clinical practice was sitagliptin, followed by vildagliptin and saxagliptin. Sitagliptin received US Food and Drug Administration approval in October 2006 and received European Medicines Agency approval in March 2007. It is licensed at the recommended dose of 100 mg once daily either as monotherapy or in combination. As monotherapy, the indication in the US is as an adjunct to diet and exercise to improve glycemic control in patients with T2DM, whereas in the EU, sitagliptin is indicated as monotherapy in patients who have inadequate glycemic control with diet and exercise and in whom metformin is inappropriate due to contraindications or intolerance. Sitagliptin is also indicated, both in the US and in EU, in combination therapy with metformin, a sulfonyleurea, or a thiazolidinedione in patients who have inadequate control with these agents used as single agents plus diet and exercise. Recently, sitagliptin was also approved

to be used in combination with insulin. Sitagliptin is also indicated as a triple therapy in combination with metformin plus a sulfonyleurea, or metformin plus a thiazolidinedione, in patients who have inadequate glycemic control with the two agents (Table 1).¹⁴ Vildagliptin was approved by the European Medicines Agency in July 2007 and it is licensed at the recommended dose of 50 mg twice a day in combination with either metformin or sulfonyleureas or thiazolidinediones in patients poorly controlled on the maximum doses of these drugs (Table 1).¹⁵ Saxagliptin, the last addition to the family of DPP-4 inhibitors, is administered at the recommended dose of 5 mg once daily in combination with metformin, or sulfonyleureas or a thiazolidinedione (Table 1).¹⁵ The mechanism of action of the DPP-4 inhibitors is complementary to that of metformin, which improves insulin sensitivity and reduces hepatic glucose production,¹² for this reason this combination can be very useful in the clinical practice, to achieve an adequate glycemic control. The aim of this review was to evaluate the clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes.

Material and methods

A systematic search strategy was developed to identify randomized controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 1996 through March 2011) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, United Kingdom). The terms “DPP-4 inhibitors”, “saxagliptin”, “metformin”, “combination saxagliptin/metformin”, “fixed dose of saxagliptin/metformin” were incorporated into an electronic search strategy that included the Dickersin filter for randomized controlled trials.¹⁶ It was also discovered that some reports have only been published in languages other than English. To avoid problems and limitations with the translation of these reports, it was decided to perform this review by including only studies published in English. The bibliographies of all identified randomized trials and review articles were reviewed to look for additional studies of interest. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to be randomized trials comparing a fixed dose of saxagliptin/metformin combination with any other oral antidiabetic drug in type 2 diabetic patients. Eligible trials had to present results on glycemic control, insulin resistance, insulin sensitivity and adverse events. Two different outcomes related to glycemic control improvement were of primary interest: (1) the proportion of individuals within each treatment group achieving clinically significant

Table 1 DPP-4 agonists: dosage and use

Drug	Dosage	Use
Sitagliptin	100 mg once daily	As an adjunct to diet and exercise to improve glycemic control as an add-on therapy to: <ul style="list-style-type: none"> • metformin (dual therapy) • sulfonylurea (dual therapy) • pioglitazone (dual therapy) • sulfonylurea plus metformin (triple therapy) • pioglitazone plus metformin (triple therapy) • In the US as monotherapy; in the EU as monotherapy in patients in whom metformin is inappropriate due to contraindications or intolerance • Insulin (with or without metformin)
Vildagliptin	50 mg twice daily	As an adjunct to diet and exercise to improve glycemic control as an add-on therapy to: <ul style="list-style-type: none"> • metformin (dual therapy) • sulfonylurea (dual therapy): in that case vildagliptin should be used at the dosage of 50 mg/day • pioglitazone (dual therapy)
Saxagliptin	5 mg once daily	As an adjunct to diet and exercise to improve glycemic control as an add-on therapy to: <ul style="list-style-type: none"> • metformin (dual therapy) • sulfonylurea (dual therapy) • pioglitazone (dual therapy)

HbA_{1c} reduction, and (2) the mean amount decrease (in%) within each treatment group. Variations in insulin resistance and insulin sensitivity that occurred during various trials were secondary outcomes of interest, as was the frequency of patients having one or more adverse events such as hypoglycemia. A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomization (0–2 points), double-blinding (0–2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5. A score above 3 indicated a study of high quality and study selection was restricted to randomized controlled trials to ensure the inclusion of only high quality evidence.¹⁷

Chemical structure, including key PK/PD data

Saxagliptin (BMS-477118; (S)-3 hydroxyadamantylglycine-L-cis-4,5 methanoproline nitrile) is a nitrile-containing DPP-4 inhibitor, with the molecular formula C₁₈H₂₇N₃O₃ and a molecular weight of 333.4 Da. It is a potent inhibitor of DPP-4 (inhibition constant, Ki = 0.6–1.3 nM) that displays slow-binding properties. Thus, kinetic studies have suggested that inhibition of DPP-4 by saxagliptin is a two-step process that involves formation of a reversible covalent enzyme inhibitor complex, in which there is a slow onset of inhibition and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms.^{18,19} Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to

off-white crystalline compound with a molecular formula of C₄H₁₁N₅HCl and a molecular weight of 165.63 Da. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Efficacy studies with saxagliptin/metformin

For a summary of the following studies, see Table 2.

Saxagliptin/metformin as initial therapy

Pfützner et al assessed the efficacy and safety of saxagliptin/metformin combination therapy compared with saxagliptin or metformin alone over 24 and 76 weeks in treatment-naïve T2DM patients with inadequate glycemic control.^{20,21} One thousand, three hundred and six patients, 18–77 years of age (HbA_{1c} 8.0%–12.0%), were randomized to saxagliptin/metformin 5/500 mg, saxagliptin/metformin 10/500 mg, 10 mg saxagliptin/placebo or 500 mg metformin/placebo. At week 76, adjusted mean changes (95% CI) from baseline HbA_{1c} were –2.31% (–2.44, –2.18) for saxagliptin/metformin 5/500 mg, –2.33% (–2.46, –2.20) for saxagliptin/metformin 10/500 mg, –1.55% (–1.70, –1.40) for saxagliptin 10 mg and –1.79% (–1.93, –1.65) for metformin 500 mg (*P* < 0.0001 versus metformin and saxagliptin monotherapies for saxagliptin/metformin 5/500 mg and saxagliptin/metformin 10/500 mg). A higher proportion of patients achieved a HbA_{1c} < 7% at week 76 with saxagliptin/metformin 5/500 mg and saxagliptin/metformin

Table 2 summary of the studies included in the review

Study	Duration	Drugs involved	Baseline population	Results
Pfützner et al ^{20,21}	76 weeks	<ul style="list-style-type: none"> • saxagliptin/metformin 5/500 mg • saxagliptin/metformin 10/500 mg • saxagliptin 10 g/placebo • metformin 500 mg/placebo. 	1306 patients, 18–77 years of age with HbA _{1c} 8.0%–12.0%.	HbA_{1c}: <ul style="list-style-type: none"> • –2.31% for saxagliptin/metformin 5/500 mg* • –2.33% for saxagliptin/metformin 10/500 mg* • –1.55% for saxagliptin 10 mg • –1.79% for metformin 500 mg (*P < 0.0001 versus metformin and saxagliptin monotherapies)
Scheen et al ²²	18 weeks	<ul style="list-style-type: none"> • saxagliptin 5 mg once daily as add on therapy to previously taken metformin • sitagliptin 100 mg once daily as add-on therapy to previously taken metformin. 	801 patients with HbA _{1c} between 6.5%–10% on stable metformin doses (1500–3000 mg/day).	HbA_{1c}: <ul style="list-style-type: none"> • –0.52% for saxagliptin/metformin • –0.62% for sitagliptin/metformin (P not significant)
De Fronzo et al ²³	24 weeks	<ul style="list-style-type: none"> • saxagliptin 2.5 mg once daily as add on therapy to previously taken metformin • saxagliptin 5 mg once daily as add on therapy to previously taken metformin • saxagliptin 10 mg once daily as add on therapy to previously taken metformin • placebo as add on therapy to previously taken metformin. 	743 patients taking a stable dose of metformin (1.500 but not >2.550 mg/day)	HbA_{1c}: <ul style="list-style-type: none"> • –0.59% for saxagliptin 2.5 mg/metformin* • –0.69% for saxagliptin 5 mg/metformin* • –0.58% for saxagliptin 10 mg/metformin* • +0.13% for placebo/metformin (*P ≤ 0.0001 versus placebo)
Goke et al ²⁴	52 weeks	<ul style="list-style-type: none"> • saxagliptin 5 mg once daily as add on therapy to previously taken metformin • glipizide up-titrated as needed from 5 to 20 mg/day as add on therapy to previously taken metformin. 	858 patients on stable metformin doses ≥ 1500 mg/day	HbA_{1c}: <ul style="list-style-type: none"> • –0.74% for saxagliptin/metformin • –0.80% for glipizide/metformin (P not significant) Hypoglycemia: <ul style="list-style-type: none"> • 3% for saxagliptin/metformin* • 36.3% for glipizide/metformin (*P < 0.0001 versus glipizide/metformin) Body weight: <ul style="list-style-type: none"> • –1.1 kg for saxagliptin/metformin* • +1.1 kg for with glipizide/metformin (*P < 0.0001 versus glipizide/metformin)

10/500 mg than with either agent alone. Similarly, a higher proportion of patients achieved a HbA_{1c} < 6.5% at week 76 with saxagliptin/metformin 5/500 mg and saxagliptin/metformin 10/500 mg than with either agent alone. For FPG at week 76, saxagliptin/metformin 5/500 mg and saxagliptin/metformin 10/500 mg groups had similar results (–54 ± 2.6 and –55 ± 2.6 mg/dL, respectively), while changes for the monotherapy groups were smaller (–24 ± 3.0 mg/dL for

saxagliptin 10 mg and –40 ± 2.8 mg/dL for metformin). For post-prandial glucose (PPG) at week 76, adjusted mean decrease from baseline was: –137 ± 5.6 mg/dL with saxagliptin/metformin 5/500 mg; –129 ± 5.9 mg/dL with saxagliptin/metformin 10/500 mg; –94 ± 6.6 mg/dL with saxagliptin monotherapy; and –86 ± 5.9 mg/dL with metformin/placebo. Changes with saxagliptin/metformin combination were greater than either monotherapy. Small decreases in

mean body weight were observed in all treatment groups. The safety profile was similar across treatment groups: in particular the overall frequency of hypoglycemic events was low (4.7% with saxagliptin/metformin 5/500 mg, 6.8% with saxagliptin/metformin 10/500 mg, 2.1% with saxagliptin 10 mg, and 6.1% with metformin alone).

Saxagliptin as add-on therapy to metformin

Scheen et al compared the efficacy of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in 801 patients with HbA_{1c} between 6.5%–10% on stable metformin doses (1500–3000 mg/day).²² Patients were randomized to add-on 5 mg saxagliptin or 100 mg sitagliptin once daily for 18 weeks. The addition of saxagliptin or sitagliptin to metformin therapy produced similar decreases in mean HbA_{1c} from baseline to week 18. Mean HbA_{1c} declined from 7.68 to 7.16% in the saxagliptin/metformin group; the adjusted mean \pm SE change was $-0.52\% \pm 0.039$ (95% CI, -0.60 to -0.45%). Similarly, mean HbA_{1c} declined from 7.69 to 7.07% in the sitagliptin/metformin group, an adjusted mean change of $-0.62\% \pm 0.038$ (95% CI, -0.69 to -0.54%). The proportion of patients achieving therapeutic glycemic responses was similar in the two treatment groups. Overall, 105 of 399 patients (26.3%) who received saxagliptin/metformin compared with 114 of 392 patients (29.1%) who received sitagliptin/metformin achieved a HbA_{1c} \leq 6.5% at week 18. For those with a HbA_{1c} \geq 7.0% at baseline, 97 of 294 patients (33.0%) in the saxagliptin/metformin group and 117 of 299 patients (39.1%) in the sitagliptin/metformin group achieved a HbA_{1c} $<$ 7.0% at week 18, a -6.1% difference between groups (95% CI, -13.8 to 1.6%). Improvements in glycemic control were also observed as decreases in FPG from baseline to week 18. Adding saxagliptin or sitagliptin to metformin therapy produced adjusted mean changes in FPG of -0.60 mmol/L (-10.8 mg/dL) and -0.90 mmol/L (-16.2 mg/dL), respectively. The mean difference was 0.30 mmol/L (5.42 mg/dL); 95% CI, 0.08 – 0.53 mmol/L (1.37 – 9.47 mg/dL). There were no apparent differences between treatment groups for the changes from baseline in fasting insulin, glucagon, proinsulin, or C-peptide. Similarly, the small improvement in β -cell function, as measured by the change from baseline in homeostasis model assessment-2 β (HOMA-2 β), did not differ between the two treatment groups. The safety profile of the two combinations was similar: in particular, hypoglycemic adverse events

occurred in 13 patients (3.2%) in the saxagliptin/metformin group and in 11 patients (2.8%) in the sitagliptin/metformin group.

De Fronzo et al²³ evaluated the efficacy of combination of saxagliptin added to metformin compared to metformin alone in a 24-week randomized, double-blind, placebo-controlled trial. Seven hundred and forty three patients taking a stable dose of metformin (1.500 but not $>$ 2.550 mg/day) for at least 8 weeks before screening, were randomized to add 2.5, 5, or 10 mg saxagliptin or placebo for 24 weeks in addition to their lead-in dose of open-label metformin.²³ At week 24, treatment with saxagliptin led to clinically and statistically significant reductions in HbA_{1c} from baseline versus metformin/placebo. Differences in adjusted mean change from baseline versus placebo (95% CI) were -0.73% (-0.92 to -0.53) for the combination 2.5 mg saxagliptin/metformin, -0.83% (-1.02 to -0.63) for the combination 5 mg saxagliptin/metformin, and -0.72% (-0.91 to -0.52) for the combination 10 mg saxagliptin/metformin, respectively (all $P < 0.0001$). Glycated hemoglobin reductions relative to metformin/placebo occurred in all saxagliptin treatment groups by week 4, the earliest time point assessed. Maximal HbA_{1c} reductions were reached at 12 weeks and were sustained through 24 weeks. The percentage of patients achieving HbA_{1c} $<$ 7.0% was comparable for 5 and 10 mg saxagliptin and higher than that for 2.5 mg saxagliptin. A greater percentage of patients taking saxagliptin achieved HbA_{1c} $<$ 7.0% versus those taking metformin/placebo. The differences from metformin/placebo (95% CI) were: 20.5% (10.6–30.5) for the combination 2.5 mg saxagliptin/metformin; 27.0% (17.0–36.7) for the combination 5 mg saxagliptin/metformin; and 27.9% (17.7–37.7) for the combination 10 mg saxagliptin/metformin, respectively (all $P < 0.0001$). Statistically significant FPG reductions at week 24 were observed in all saxagliptin treatment groups versus the metformin/placebo group ($P < 0.0001$). Differences in adjusted mean change from baseline versus metformin/placebo (95% CI) were: -15.6 mg/dL (-22.5 to -8.5) for the combination 2.5 mg saxagliptin/metformin; -23.3 mg/dL (-30.3 to -16.3) for the combination 5 mg saxagliptin/metformin; and -21.7 mg/dL (-28.8 to -14.7) for the combination 10 mg saxagliptin/metformin, respectively. Differences between the effects of saxagliptin and metformin/placebo on mean FPG were apparent and near maximal as early as week 2 in all saxagliptin treatment groups, with the effect maintained throughout 24 weeks. The early insulin response based on the insulinogenic index, and insulin sensitivity, increased in all saxagliptin treatment groups at week 24. The overall frequency of confirmed hypoglycemia during the 24-week treatment period was similar for saxagliptin-treated

patients (0.5%) and metformin/placebo-treated patients (0.6%). No dose relationship was observed among the three saxagliptin groups.

Goke et al assessed the efficacy and safety of saxagliptin compared to glipizide as add-on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone.²⁴ A total of 858 patients on stable metformin doses ≥ 1500 mg/day were randomised to saxagliptin 5 mg/day or glipizide up-titrated as needed from 5 to 20 mg/day for 52 weeks. At 52 weeks, saxagliptin/metformin was non-inferior to glipizide/metformin in lowering HbA_{1c}. Adjusted mean changes from baseline HbA_{1c} were -0.74% with saxagliptin/metformin and -0.80% glipizide/metformin, respectively; the between-group difference was 0.06% (95% CI 0.05% to 0.16%). The proportion of patients reporting ≥ 1 hypoglycemic event over 52 weeks was low in the saxagliptin/metformin group (3.0%), and was significantly lower compared with the glipizide/metformin group (36.3%) (difference versus glipizide/metformin -33.2% (95% CI, -38.1% to -28.5% ; $P < 0.0001$). Treatment with saxagliptin was associated with an adjusted mean change in body weight from baseline of -1.1 kg with saxagliptin and $+1.1$ kg, with glipizide, respectively; the between-group difference was -2.2 kg (95% CI, -2.7 to -1.7 ; $P < 0.0001$). There was a small rise per week in HbA_{1c} during weeks 24–52 in both treatment groups (mean changes per week 0.001% for saxagliptin and 0.004% for glipizide). The rise per week was statistically significantly smaller with saxagliptin versus glipizide (-0.002% difference, 95% CI, -0.0046% to -0.0001% ; $P = 0.04$) indicating a more sustained effect on glycemic control beyond week 24. There were small and generally similar increases from baseline in both treatment groups in mean values for fasting insulin and fasting C-peptide. Numerical reductions in fasting proinsulin (mean difference versus glipizide/metformin -5.5 ± 1.67) and numerically smaller increases in fasting glucagon (mean difference versus glipizide/metformin -4.9 ± 1.88) were demonstrated for saxagliptin versus glipizide. Patients treated with glipizide/metformin had a greater mean increase in HOMA-2 β ($+21.7 \pm 2.56$) versus saxagliptin/metformin ($+7.4 \pm 2.54$).

Safety and tolerability

Generally, saxagliptin has been reported to be well tolerated in clinical studies. The most common adverse events reported in patients receiving combination therapy and occurring more commonly than with metformin alone included headache (7.5% versus 5.2%), nasopharyngitis (6.9% versus

4.0%), upper respiratory tract infection, and urinary tract infection.²⁵

Coadministration of strong cytochrome P 450 isoenzyme 3 A4/5 inhibitors (eg, ketoconazole) significantly increases saxagliptin concentrations, necessitating dose limitations to 2.5 mg/1000 mg once daily. Lower doses of concomitantly administered sulfonylureas may be needed to reduce the risk for saxagliptin-related hypoglycemia.

Metformin-related adverse events include diarrhea and nausea/vomiting; because of the metformin-related risk for lactic acidosis, patients should be warned against excessive alcohol intake. Treatment with saxagliptin/metformin is not recommended in hepatic impairment and contraindicated in renal impairment. Renal function should be monitored before initiation of therapy and at least annually thereafter; more frequent assessments are recommended for patients at risk of renal impairment, such as the elderly. Treatment should be temporarily discontinued in patients undergoing radiologic studies with intravascularly administered iodinated contrast materials, and those undergoing surgical procedures associated with restricted intake of food and fluids.

Hypoglycemia

Hypoglycemia was reported in 3.4% of treatment-naive patients receiving saxagliptin 5 mg/metformin combination therapy compared with 4.0% of those receiving metformin alone. Among treatment-experienced patients, the incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg with metformin was 7.8% and 5.8%, respectively, compared with 5.0% for those receiving metformin monotherapy.

Compared to the sulfonylureas, saxagliptin gave a low incidence of hypoglycemia, as reported by Goke et al.²⁴ Three percent of patients in the saxagliptin/metformin group and 36.3% of patients in the glipizide/metformin group experienced hypoglycemic events over the 52-week treatment period. Most hypoglycemic events were mild in intensity; 0.2% of patients in the saxagliptin/metformin group and 14.4% of patients in the glipizide/metformin group had hypoglycemic events that were moderate in intensity. No patients in the saxagliptin/metformin group and 1.6% of patients in the glipizide/metformin group had hypoglycemic events that were severe. No patients in the saxagliptin/metformin group and 0.9% of patients in the glipizide/metformin group experienced a mild hypoglycemic adverse event requiring medical assistance.

Patient perspectives

In November 2010, the US Food and Drug Administration (FDA) approved the first and only once-daily combination

tablet featuring saxagliptin and extended-release (XR) metformin HCl to improve glycemic control in adults with type 2 diabetes mellitus. Saxagliptin/metformin XR is available in 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg strengths. The starting dose should be individualized based on the patient's current regimen and administered with the evening meal, with gradual dose titration to decrease the risk for metformin-related gastrointestinal events (maximum dose, 5 mg/2000 mg). This prescription provides good acceptability for patients with T2DM, who are commonly treated with a large number of drugs. This fixed dose combination also allows physicians to increase the antidiabetic therapy in patients not well controlled by metformin alone without increasing the number of pills taken by the patients, improving patient compliance. The combination of saxagliptin/metformin proved to be safer than combinations of sulfonylureas/metformin with respect to hypoglycemic events.²⁴ This aspect is very important: hypoglycemia can be very dangerous in patients with coronary disease because of the risk of triggering a heart attack, and in older people because of the risk of falls. Also, the saxagliptin/metformin combination proved to be neutral or even positive with respect to body weight gain, and this is another advantage of this combination.²⁴

Conclusion and place in therapy

The studies reported above showed that the combination of saxagliptin/metformin was well tolerated and produced sustained glycemic control for up to 76 weeks, with greater improvements in glycemic parameters when compared with either drug alone.²⁰ These results are generally similar to those obtained with the other two DPP-4 inhibitors, sitagliptin^{26,27} and vildagliptin.²⁸ At 1 year, the least squares reduction from baseline results of HbA_{1c} was greater for sitagliptin/metformin 100/2000 mg (−1.9%) than for metformin 2000 mg alone (−1.6%).²⁶ At 2 years, the initial combination reduction (−1.7%) remained greater than that for metformin alone (−1.3%). Other glycemic measures were consistent with the HbA_{1c} results.²⁷ For vildagliptin, there was a 24 week study which compared vildagliptin combined with high-dose metformin combination therapy (50/1000 mg twice daily), vildagliptin combined with low-dose metformin combination therapy (50/500 mg twice daily), vildagliptin monotherapy (50 mg twice daily) and high-dose metformin monotherapy (1000 mg twice daily).²⁸ From comparable baseline values (8.6%–8.7%), HbA_{1c} decreased in all four treatment groups, to the greatest extent with vildagliptin/metformin 50/1000 mg twice daily. Mean HbA_{1c} change from

baseline was: $-1.8\% \pm 0.06\%$ with vildagliptin/metformin 50/1000 mg twice daily; $-1.6\% \pm 0.06\%$ with vildagliptin/metformin 50/500 mg twice daily; $-1.1\% \pm 0.06\%$ with vildagliptin monotherapy (50 mg twice daily); and $-1.4\% \pm 0.06\%$ with high-dose metformin monotherapy (1000 mg twice daily). The between-group difference was superior with vildagliptin/metformin 50/1000 mg twice daily combination therapy ($P < 0.001$ versus both monotherapies) and vildagliptin/metformin 50/500 mg twice daily combination therapy ($P < 0.001$ and $P = 0.004$, versus vildagliptin and metformin monotherapies, respectively). There was no incidence of hypoglycemia or severe hypoglycemia with either combination therapy, and neither was associated with weight gain. All treatments were well tolerated and displayed a comparable incidence of adverse events overall. Our group²⁹ conducted a study on sitagliptin, where we compared sitagliptin/pioglitazone 100/30 mg once a day and metformin/pioglitazone 850/15 mg twice a day. After 12 months of treatment we showed that the addition of either sitagliptin or metformin to pioglitazone gave an improvement in HbA_{1c}, FPG, and PPG; but metformin led also to a decrease in body weight and to a faster and better improvement of insulin resistance and inflammatory state parameters, even if sitagliptin gave a better protection of beta-cell function.²⁹ We have also conducted a study on vildagliptin comparing either pioglitazone 30 mg once a day plus vildagliptin 50 mg twice a day or glimepiride 2 mg 3 times a day plus vildagliptin 50 mg twice a day. We observed that, after 12 months, the pioglitazone/vildagliptin combination was more effective in preserving beta-cell function, and in reducing insulin resistance and inflammatory state parameters than vildagliptin/glimepiride.³⁰ The positive effect on insulin resistance is very important given that the main mechanism of T2DM is insulin resistance.

When directly compared to other DPP-4 inhibitors such as sitagliptin, saxagliptin showed its non-inferiority when added to metformin therapy in lowering HbA_{1c}. Saxagliptin was generally well tolerated in patients with T2DM whose glycemia was inadequately controlled by metformin alone.¹⁹ Saxagliptin proved also its non-inferiority compared to sulfonylureas in the study conducted by Goke et al where saxagliptin/metformin combination was well tolerated, provided a sustained HbA_{1c} reduction over 52 weeks, reduced body weight and a significantly lower risk of hypoglycemia.²⁴ Furthermore, patients treated with glipizide plus metformin had a greater mean increase in HOMA-2 β , proving once again the protective effect of DPP-4 inhibitors, and in particular saxagliptin, on β -cell.²⁴

Clinical practice recommendations for the treatment of T2DM advocate lifestyle interventions (dietary modification, increased exercise, weight loss) together with starting metformin treatment at the time that the T2DM is diagnosed.¹ Once metformin fails to maintain glycemic control another antidiabetic drug should be added. In this setting, DPP-4 inhibitors should be the logical choice because of their comparable effects on HbA_{1c} compared to the addition of a sulfonylurea^{31,32} or glitazone,^{33,34} and because of their positive effects on beta cell function and their neutral effects on body weight. DPP-4 inhibitors are particularly indicated in young patients, with a long life expectancy, because of the protective effect on β -cell function. While sulfonylureas increase HOMA-2 β and proinsulin,²⁴ DPP-4 inhibitors reduce them, granting a longer survival of β -cells.²⁹ DPP-4 inhibitors also reduce insulin resistance, decreasing HOMA-IR,^{29,30} and they also prevent the risk of hypoglycemia posed by sulfonylureas. This makes these drugs safer in elderly patients.³⁵

In summary

- When diet and exercise are not enough to produce adequate glycemic control, metformin should be added
- When diet, exercise, and metformin are not enough, a combination therapy should be started. DPP-4 inhibitors could be a good choice
- DPP-4 inhibitors, and in particular saxagliptin, showed their non-inferiority compared to sulfonylureas in improving HbA_{1c}
- DPP-4 inhibitors, in particular saxagliptin, gave a lower incidence of hypoglycemic events compared to sulfonylureas
- The combination of saxagliptin/metformin proved to have a positive effect on body weight.

Disclosure

The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

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