LIBERTAS Academica
FREEDOM TO RESEARCH

REVIEW

Saxagliptin and Metformin in Fixed Combination for the Treatment of Type 2 Diabetes in Adults

Molly G. Minze, Mary S. Klein and Brian T. Terrell

School of Pharmacy, Texas Tech University Health Sciences Center, Abilene, Texas.
Corresponding author email: molly.minze@ttuhsc.edu

Abstract: Type 2 diabetes affects millions of people worldwide and significantly contributes to morbidity and mortality of those affected by it. Current guidelines recommend individualized treatment regimens following first line metformin therapy. Saxagliptin, a dipeptidyl-peptidase 4 inhibitor, provides a secondary mechanism of action to decrease hyperglycemia when used in combination with metformin. The combination of metformin and saxagliptin has shown improvements in hemoglobin A_{1c} and fasting plasma glucose in greater efficacy than when either agent is used alone. Adverse effects of combination therapy are similar to when these agents are used individually, and are rated as tolerable by patient satisfaction scores. Overall, the combination use of saxagliptin in addition to metformin is an attractive option for clinicians to use in the treatment of type 2 diabetes.

Keywords: saxagliptin, metformin, type 2 diabetes combination therapy

Introduction

Diabetes affects approximately 26 million people in the United States. It is a leading cause of morbidities including new onset blindness, kidney failure, and non-traumatic limb amputation, and is a significant cause of heart disease and stroke.[1,2] Specifically, the International Diabetes Federation estimates 440 million people to have diabetes by the year 2010, and type 2 diabetes is estimated to more than triple in prevalence by the year 2050.[2,3] Because of this high prevalence, morbidity, and mortality, many pharmacotherapeutic treatment options with varying mechanisms of action have been developed to reduce hyperglycemia. The American Diabetes Association/European Association for the Study of Diabetes now recommends an individualized approach to the treatment of type 2 diabetes, allowing individual patient and disease factors to specifically drive a clinician's choice of therapy for each patient.[5] With this individualized approach to therapy, there are many pharmacologic entities a clinician may choose in creating an individualized treatment plan. Even with current therapies available, less than half of patients achieve the hemoglobin A_{1c} target of less than 7.0%.[4] Recently, new target therapies focusing on combination mechanisms provide novel treatment approaches for patients with uncontrolled type 2 diabetes. The saxagliptin-metformin combination therapy provides an approach comprised of differing mechanisms which focus on a first line therapy of metformin, which targets insulin resistance while maintaining weight neutrality, along with reduction of hyperglycemia in a postprandial state through saxagliptin.

Pathophysiology of Type 2 Diabetes

Diabetes mellitus results from the impairment of insulin action on carbohydrate, protein, and fat metabolism.[6] Type 2 diabetes manifests mechanistically in the form of insulin resistance and impaired insulin secretion.[6,7] Insulin resistance occurs from the reduced ability of adipose and muscle cells to transport glucose intracellularly for use, coupled with the inability of insulin to decrease suppression of hepatic glucose production.[7,8] Impaired insulin secretion results from the beta-cell's inability to compensate for elevations in blood glucose and overcome the insulin resistance.[6,9–11] Euglycemia is maintained until beta-cell number and secretory capacity decline.[2] At diagnosis, there is an estimated 50% reduction in the capacity of beta-cell function, thus leading to either impaired fasting glucose or impaired glucose tolerance.[2,11] Beta-cell decline is further deteriorated and progressively worsened despite treatment, secondary to chronic elevations in blood glucose (glucotoxicity), exposure to free fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation, signaling apoptosis of beta-cells.[2,3,11,12] In addition, pancreatic alpha-cells hyper secrete glucagon only to further increase the hepatic production of glucose.[5] Ultimately, patients with type 2 diabetes are at risk of developing long-term complications including cardiovascular disease, coronary artery disease, stroke, and peripheral vascular disease (macrovascular complications), in addition to nephropathy, neuropathy, and retinopathy (microvascular complications).[13,14]

Recently, understanding of the mechanism surrounding the incretin hormones within the gut have led to the development of several oral and injectable incretin-like medications which focus on pharmacotherapy targeting of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[12] The incretin effect in healthy individuals allows for insulin secretion in response to oral uptake of glucose. An estimated 70% of insulin secretion occurs in response to this oral mechanism. This secretion is not matched when glucose is administered intravenously. This mechanism of insulin section is associated with both GLP-1 and GIP, as both hormones enter circulation subsequent to oral glucose absorption. GIP is secreted within the proximal small intestine subsequent to an oral glucose load, but is quickly degraded by dipeptidyl-peptidase-4 (DPP-4) after approximately 5 to 7 minutes. Patients with type 2 diabetes have a reduced sensitivity to this glucose-induced insulin secretion. However, patients with type 2 diabetes have a preserved insulinotropic response to GLP-1, which is secreted by the jejunum, ileum, and colon within minutes of eating. Treatment with GLP-1 in patients with type 2 diabetes increased fasting and mealtime insulin levels, decreases fasting plasma glucose, and suppresses postprandial hyperglycemia. Other beneficial actions of GLP-1 include increased satiety secondary to a delay in gastric emptying, reduction in glucagon release

from alpha-cells, increased glycogen production by hepatocytes, protection of beta-cells from apoptosis secondary to hyperglycemia, and hyperlipidemia.[10,12] Like GIP, GLP-1 is quickly inactivated by DPP-4, and it is estimated that over half of GLP-1 is inactivated before entering systemic circulation.[12] Moreover, the half-life of GLP-1 is less than 2 minutes.[12]

Because of the actions and benefits discussed above, the incretin system provides a promising mechanism for therapies to treat type 2 diabetes. Exogenous GLP-1 therapies, such as exenatide and liraglutide, have been developed and are indicated for the treatment of type 2 diabetes. Secondary to the short half life of GLP-1, therapeutic strategies inhibiting the degradation of GLP-1 have emerged to enhance endogenous GLP-1.[10] Inhibition of the DPP-4 enzyme, which inactivates GLP-1, is a novel target for therapy for type 2 diabetes.[10,12] Examples of DPP-4 inhibitor pharmacotherapies approved in the US include sitagliptin, saxagliptin, and linagliptin, while vildagliptin has been approved in Europe and Latin America.[15]

Metformin is a longstanding treatment for type 2 diabetes and is the recommended first line treatment for type 2 diabetes.[2,5] Metformin was first understood to be integral in treating hyperglycemia in the UKPDS trial, where patients had a reduction in myocardial infarctions and death from any cause.[16] Because of this, metformin is theorized to provide more cardiovascular protection than any other medication used in the treatment of type 2 diabetes.[17] In addition to the cardiovascular benefit exhibited by patients who receive metformin therapy, metformin also is weight neutral in that it does not cause weight gain, and rarely is associated with hypoglycemia when used as monotherapy.[2] A drawback to metformin use includes that it is associated with gastrointestinal effects, including diarrhea, especially when initiating therapy at higher doses.[2,5]

Overtime, patients with type 2 diabetes require more than one agent to control blood glucose.[5,18] When a patient requires two oral medications to control fasting and post prandial blood glucose, the pharmacotherapy choices must be tailored to patient specific needs and be agents with different mechanisms of action.[5,19,20] Kombiglyze™ XR (saxagliptin/metformin XR) is a combination product used in conjunction with diet and exercise to treat type 2 diabetes.[21] This review discusses the use of the combination saxagliptin/metformin for the treatment of type 2 diabetes.

Mechanism of Action and Pharmacokinetics
Saxagliptin
Mechanism of action
Saxagliptin is a selective, reversible, and competitive DPP-4 inhibitor.[22,23] The incretin hormones, GIP and GLP-1, are released in a glucose-dependent manner in response to a meal.[22–24] These hormones, released from the small intestine, stimulate the pancreas to secrete insulin as well as decrease the secretion of glucagon.[22,24] DPP-4 rapidly inactivates the incretin hormones, decreasing their duration of action. It is present within the endothelium of various organs and has enzymatic activity in circulating plasma.[3,22,23] Inhibition of DPP-4 is an attractive therapeutic mechanism which results in increased plasma concentrations of endogenous GLP-1.[3] Saxagliptin inhibits DPP-4, precipitating an increased concentration of these endogenous hormones that ultimately lowers fasting and postprandial glucose levels in patients with type 2 diabetes.[22,23]

Pharmacokinetics
The time to concentration for saxagliptin and its active metabolite is 2 and 4 hours, with a medication duration of action of 24 hours.[22,23] Saxagliptin is a nitrile containing compound, a potent inhibitor of DPP-4, and it inhibits DPP-4 via a two-step process of first reversible covalent enzyme inhibition and secondly slow equilibration between active and inactive forms.[25] Its long duration of action is achieved via substitution of vinyl at the β-position of α-cycloalkyl-substituted glycines of DPP-4 inhibitors. Saxagliptin results from hydroxylation of the adamantyl group, leading to high in vitro and in vivo potency with good oral bioavailability and no CYP 3A4 inhibition.[3] An increase in endogenous GLP-1 is seen secondary to a high glucose load in healthy rats.[3] Clinically, when administered with a high fat meal, time to C_{max} was slightly delayed but directions indicate that saxagliptin may be given with or without meals.[22,23] The drug has little to no plasma protein binding and saxagliptin is metabolized by CYP3A4/5 to its metabolite, which is also a DPP-4 inhibitor. Although less

potent, the metabolite of saxagliptin is more selective than the parent compound.[22,23] Saxagliptin is also a P-glycoprotein substrate but does not significantly inhibit or induce P-glycoprotein.[21] Caution should be taken when administering saxagliptin or products containing saxagliptin concurrently with strong CYP3A4/5 inhibitors or inducers. However, saxagliptin is not an inhibitor of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4 and is not an inducer of CYP1A2, 2B6, 2C9, or 3A4.[21–23] The medication is eliminated by both renal (~75%) and hepatic means, necessitating a dose reduction in those patients with moderate to severe renal impairment.[22,23]

Adverse effects

In clinical practice, saxagliptin is well tolerated as monotherapy, with an adverse event rate and discontinuation rate very similar to placebo, regardless of dosage.[22] Within pooled data, the most common adverse event associated with saxagliptin alone was upper respiratory infection, urinary tract infection, and headache, although these adverse events were seen at rates similar to placebo. Additionally, few patients experience hypoglycemia when saxagliptin is administered as monotherapy.

Metformin
Mechanism of action

Metformin belongs to the biguanide class of medications with the primary mechanism of action to improve glycemic control through a decrease in hepatic glucose production.[26,27] Metformin also decreases the absorption of glucose from the gastrointestinal tract as well as increase the sensitivity of peripheral tissues to glucose.[26] The exact cellular mechanism is not completely understood but research has shown that it may be due to activation of AMP-activated protein kinase.[28–30] Additional evidence that metformin may contribute to an increase in the circulating concentration of GLP-1, further improves glycemic control.[31,32]

Pharmacokinetics

The bioavailability of metformin ranges from 50%–60% and is not significantly affected by food.[26] The time to C_{max} for the extended release formulation of metformin, the product included in the combination product Kombiglyze XR®, is about 7 hours.[21,26]

Protein binding is negligible and metformin is not hepatically metabolized.[26] As such, metformin is excreted unchanged in the urine, with tubular secretion being the primary form of elimination.[26] This route of elimination is the reason for the contraindication in patients with significantly impaired renal function.[26]

Adverse effects

Common adverse effects of metformin include gastrointestinal effects, ranging from diarrhea to constipation and nausea to vomiting, in addition to abdominal discomfort, flatulence, indigestion, and heart burn.[15,26,33] Hypoglycemia occurs rarely as monotherapy, but more frequently when metformin is used in combination therapies. It is estimated that approximately 5% of patients prescribed metformin are intolerant to the lowest dose.[33] Vitamin B_{12} malabsorption secondary to calcium-dependent antagonism in the ileal membrane occurs in approximately 10%–30% of patients. This is resolved through supplemental calcium. Additionally, vitamin B_{12} deficiency has been associated with dose and length of therapy. Other more rare and sporadic adverse effects seen with metformin therapy include leucocytoclastic vasculitis, allergic pneumonitis, cholestatic jaundice, and hemolytic anemia.[33] The most serious adverse effect with metformin therapy is lactic acidosis and is reported in up to 32% of metformin overdose cases.[26]

Pharmacokinetic effects of combination therapy

When investigating the effect of saxagliptin on the pharmacokinetics of several other oral antidiabetic agents, no clinically meaningful changes to metformin pharmacokinetics were noted.[34] However, metformin did lower the C_{max} of saxagliptin by 21%, although the AUC values of saxagliptin were unchanged when compared to saxagliptin administered alone.[34] The authors concluded that this interaction was not clinically significant and no dose alterations are recommended when both drugs are administered concurrently.[21,34]

Adverse effects of combination

Using metformin and saxagliptin in combination provides similar adverse effect profiles as seen with these pharmacologic agents as monotherapy. In treatment

naïve patients, headache and nasopharyngitis were two adverse effects seen more often in patients who took saxagliptin 5 mg in addition to metformin, versus placebo in addition to metformin.[21] Both groups experienced similar incidences of diarrhea as metformin therapy was present in both groups. Hypoglycemia was experienced with a slight increase in the saxagliptin 2.5 mg plus metformin (7.8%), than the saxagliptin 5 mg plus metformin (5.8%), or the placebo plus metformin group (5%). Other adverse effects seen when the individual drug therapies were studied or are prec = sceie = bed have not been observed within the literature.

Clinical Trials

A Medline search of clinical trials using the search terms saxagliptin, metformin, combination, fixed dose combination, and type 2 diabetes was completed. Additionally, a search of clinicaltrials. gov was performed using the search terms saxagliptin and metformin.

No trials evaluating the safety and efficacy of a fixed dose combination of saxagliptin and metformin in type two diabetes were available at the time of search.[21] Bioequivalence studies determined a fixed dose combination of saxagliptin and metformin and extended release are equivalent to the extended release of metformin and saxagliptin individually.[35] Trials comparing a fixed dose extended release metformin and saxagliptin combination with immediate release metformin and saxagliptin individually, however, have not been performed.[35]

Efficacy and safety trials

A 24 week multicenter, randomized, double-blind, active controlled trial of 1306 patients compared metformin or saxagliptin for initial treatment versus treatment with saxagliptin in combination with metformin.[36] While the trial did not use a fixed dose combination product, the study groups mimicked currently available fixed dose products. The primary outcome of the trial was the change in HbA_{1c} from baseline to 24 weeks across each of the study groups. Key secondary endpoints included the change in fasting plasma glucose and the proportion of patients achieving HbA_{1c} of less than 7%. Further, the authors sought to compare safety endpoints for monotherapy versus combination therapy.

Type 2 diabetes treatment naïve patients ages 18–77 years old who had an A_{1c} between 8% and 12%, a fasting C peptide of greater than 1 ng/mL, and body mass index of less than 40 were included in the trial.[36] Conversely, patients were excluded if they had a history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, a cardiovascular event within six months of study entry, New York Heart Association Class III or IV congestive heart failure and/or left ventricular ejection fraction of less than 40%, or a history of alcohol or drug abuse. Individuals with renal, liver, or psychiatric disease, treatment with CYP 3A4 inhibitors or inducers, or were on insulin therapy within a year of study screening were also omitted.

The patients received treatment of either saxagliptin 5 mg plus metformin 500 mg daily (n = 320), saxagliptin 10 mg plus metformin 500 mg daily (n = 323), saxagliptin 10 mg daily plus placebo (n = 335), or metformin 500 mg daily plus placebo (n = 328).[36] Last observation carried forward method was used to analyze the results. Metformin dosing was titrated based on achieving fasting plasma glucose of less than 110 mg/dL and a maximum of 2000 mg metformin for all groups receiving it. At study completion, the total daily dose of metformin received across each group was similar.

At baseline, average age was 52 years old and patients were evenly split between male and female. Patients had an average HbA_{1c} across all groups of 9.4%–9.6%, and an average BMI of 30%.[36] 98.4% of patients in the trial were completely treatment naïve at the beginning of the study. The authors found that use of saxagliptin 5 mg or 10 mg in combination with metformin significantly decreased HbA_{1c} and fasting plasma glucose when compared with either drug as monotherapy. At 24 weeks, both saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin decreased HbA_{1c} by 2.5%, while saxagliptin 10 mg alone reduced HbA_{1c} by 1.7% ($P < 0.0001$), and metformin alone decreased HbA_{1c} by 2.0% ($P < 0.0001$). Patients with higher HbA_{1c} values at baseline saw greater decreases than those with lower HbA_{1c}. Significantly more patients reached the HbA_{1c} goal of <7.0% in the saxagliptin 5 mg combination group (60.3%) and the saxagliptin 10 mg combination group (59.7%) than either saxagliptin or metformin alone (32.2% and 41.1% respectively, $P < 0.0001$). Fasting plasma glucose at week 24 was decreased by

60 mg/dL from baseline in the saxagliptin 5 mg combination group and 62 mg/dL in the saxagliptin 10 mg combination group, while the saxagliptin monotherapy group decreased by 31 mg/dL and metformin monotherapy decreased by 47 mg/dL ($P < 0.0001$ for either monotherapy vs. saxagliptin 5 mg combination, $P = 0.0002$ for saxagliptin 10 mg combination versus metformin).

This study showed that initial combination therapy with saxagliptin plus metformin may produce greater A_{1c} lowering than monotherapy with either medication. The trial also highlights that there is little increase in efficacy between the 5 mg and 10 mg saxagliptin dose. This is likely the reason that the 10 mg dose is not typically used in clinical practice. Likewise, the study did not include the saxagliptin 2.5 mg plus metformin dose, which is currently available both as monotherapy and as fixed dose combination. Further, because this study was not completed using a fixed dose combination, patient compliance could vary, and therefore results would be improved if the patients took a single tablet as opposed to multiple tablets. The authors did not report medication compliance in their results.

A 76-week extension of the previously described trial was published in 2011.[37] Patients who completed all visits during the 24-week trial or who met progressive glycemic rescue criteria during the long-term trial continued their assigned treatment. Patients with an HbA_{1c} of greater than 8% at week 30, 37, or 50 or those with an HbA_{1c} greater than 7.5% at week 63 were rescued with pioglitazone 15 mg, which could be titrated up to 45 mg daily if needed. Endpoints assessed in the trial included change from baseline in HbA_{1c}, fasting plasma glucose, 2 hour postprandial glucose, proportion of patients achieving HbA_{1c} <7.0%, time to rescue therapy or discontinuation, and proportion of patients requiring rescue therapy.

888 patients began the 76 week follow-up period following the initial 24 week study, and 613 (69%) of those patients completed the follow-up period without the use of rescue medication.[37] At 76 weeks from baseline, patients receiving saxagliptin 5 mg plus metformin achieved an HbA_{1c} reduction of −2.31% (n = 177, $P < 0.0001$ versus saxagliptin 10 mg alone and metformin alone), a non-significant fasting plasma glucose reduction of −54 mg/dL versus either monotherapy (n = 154), and a non-significant postprandial

glucose reduction versus monotherapy of −137 mg/dL (n = 124). Patients receiving saxagliptin 10 mg plus metformin achieved similar decreases, with an HbA_{1c} reduction of −2.33% (n = 178, $P < 0.0001$ versus monotherapy), a non-significant fasting plasma glucose reduction of −55 mg/dL (n = 160), and a non-significant postprandial reduction of −129 mg/dL (n = 109). There was no difference between the groups in the proportion of patients that reached HbA_{1c} goal of less than 7% at 76 weeks. 27.9% of patients in the metformin plus saxagliptin 5 mg group required rescue medications prior to the end of the 76 weeks, compared with 30.9% in the saxagliptin 10 mg plus metformin group, 41.9% in the metformin alone group, and 56.1% in the saxagliptin alone.

These results show maintained HbA_{1c} control at 76 weeks in the saxagliptin 5 mg plus metformin group. However, more than a quarter of patients needed a third medication in the form of a rescue medication by the end of the trial which may cause concern for length of time that HbA_{1c} reduction can be maintained on a single combination pill alone.

Defronzo and colleagues[38] performed a four arm, randomized, double-blind, placebo-controlled study of 743 patients that sought to examine the efficacy of saxagliptin in combination with metformin in patients who were uncontrolled with metformin alone.[38] Patients included in the trial were age 18–77 years old and had uncontrolled type 2 diabetes, defined as an HbA_{1c} greater than 7% and less than 10%, and were taking metformin at doses between 1500 mg and 2550 mg for at least 8 weeks prior to study entry. Mean age in the trial was 54.6 years and the duration of diabetes diagnosis was 6.5 years. Exclusion criteria were similar to the previously described trial.

After a two week metformin only lead in period, patients were randomized to receive saxagliptin 2.5 mg (n = 192), 5 mg (n = 191), 10 mg (n = 181), or placebo (n = 179) in addition to metformin for 24 weeks.[38] The primary endpoint of the trial was the change in HbA_{1c} from baseline to 24 weeks. Key secondary endpoints included the change in fasting plasma glucose, change in postprandial glucose and the proportion of patients reaching an HbA_{1c} goal of less than 7%. For statistical analysis, all saxagliptin groups were compared with the metformin plus placebo group.

At baseline, the average HbA_{1c} and fasting plasma glucose were 8% and 176 mg/dL, respectively, across all groups.[38] At 24 weeks, patients in the saxagliptin 2.5 mg plus metformin saw an average HbA_{1c} decrease of 0.73% (−0.92% to −0.53%, $P < 0.0001$) compared with placebo. Patients in the saxagliptin 5 mg plus metformin achieved an average HbA_{1c} decrease of 0.83% (−1.02% to −0.63%, $P < 0.0001$) compared with placebo, while those in the saxagliptin 10 mg plus metformin achieved an average HbA_{1c} decrease of 0.72% (−0.91% to −0.52%, $P < 0.0001$) compared with placebo. Further, 69%, 81%, and 80% of patients in the saxagliptin 2.5 mg, 5 mg, and 10 mg groups, respectively, achieved the HbA_{1c} goal of less than 7%, compared with only 29% of those in the placebo group ($P < 0.0001$). Statistically significant reductions in fasting plasma glucose were also achieved across all saxagliptin groups, with decreases of −15.6 mg/dL (−22.5 to −8.5, $P < 0.0001$), 23.3 mg/dL (−30.3 to −16.3, $P < 0.0001$), and 21.7 mg/dL (−28.8 to −14.7, $P < 0.0001$) versus placebo seen in the saxagliptin 2.5 mg, 5 mg, and 10 mg groups, respectively. Finally all groups saw significant decrease in 2 hour postprandial blood glucose at 24 weeks, with those in the saxagliptin 2.5 mg group decreasing −43.5 mg/dL ($P < 0.0001$) versus placebo, patients in the 5 mg group decreasing −40.3 mg/dL ($P < 0.0001$), and those in the 10 mg group decreasing −31.8 mg/dL ($P < 0.0001$).

This trial highlights clinically and statistically significant improvements in HbA_{1c}, fasting plasma glucose, and postprandial glucose achieved when saxagliptin is added to metformin in non-treatment naïve patients. While results are not as clinically impressive as those seen in the previous trial, this cohort of patients had a longer duration of disease, and while other medication use was not reported, had likely been exposed to anti-hyperglycemic medications for a longer period of time than in the Jadzinsky trial.

A post-hoc analysis combined pooled data from Bristol Meyers Squibb comparing saxagliptin plus metformin to saxagliptin plus glyburide and saxagliptin plus pioglitazone in patients treated in the United States.[39] Inclusion and exclusion criteria for each trial were similar to those reported above in the Defronzo trial, and data for the saxagliptin plus metformin comparator group was taken directly from this trial.

All patients in the analysis were receiving stable background doses of metformin of at least 1500 mg daily throughout the trial.[39]

547 patients were randomized to receive saxagliptin 2.5 mg or 5 mg plus glyburide (7.5 mg or 10 mg daily titrated to 20 mg daily), or saxagliptin 2.5 mg or 5 mg plus pioglitazone (30 mg or 45 mg daily).[39] At baseline across all groups, average HbA_{1c} was 8.0%–8.4% and fasting plasma glucose ranged from 177–192 mg/dL. At 24 weeks, the authors reported no difference in HbA_{1c} reduction among the groups, though statistical analysis of the results was not published. Patients in the saxagliptin 2.5 mg and 5 mg plus metformin group achieved HbA_{1c} lowering of −0.87% and −0.89%, respectively. Those patients in the group which added glyburide achieved reductions in HbA_{1c} of −0.51% and −0.52%, respectively, while patients in the thiazolidinedione group achieved HbA_{1c} reductions of −0.45% and −0.60%. Across groups, decreases in fasting plasma glucose were −11 mg/dL and −13 mg/dL in the saxagliptin 2.5 mg and 5 mg plus glyburide groups, −14 mg/dL and −20 mg/dL in the saxagliptin 2.5 mg and 5 mg plus thiazolidinedione groups, and −15 mg/dL and −25 mg/dL for saxagliptin 2.5 mg and 5 mg plus metformin groups.

While the results provided in the post-hoc analysis lack comparative statistical analyses across the provided drug classes, the analysis does appear to show that saxagliptin plus metformin is at least equal to, and may in some cases be more effective than, saxagliptin plus glyburide or pioglitazone.

In addition to the trials above, a phase IIIb, eighteen week, randomized, double blind, multicenter trial was performed in 54 sites throughout the USA and Latin America.[18] This study compared the extended release formulation of metformin used in combination with saxagliptin versus the efficacy of uptitrating the extended release metformin. The primary endpoint of the study evaluated A_{1c} change from baseline, with secondary endpoints evaluating fasting and prost prandial blood glucose changes from baseline, proportion of patients with A_{1c} <7% at the end of the study, safety and tolerability, and patient outcomes measured via a satisfaction score sheet. The study population included patients with T2DM receiving metformin XR 850–1500 mg monotherapy, with a baseline of A_{1c} 7.5%–11%.

Patients were stabilized on a fixed dose of 1500 mg metformin XR during an 8-week lead in period.[18] Thereafter patients were randomized to treatment with saxagliptin 5 mg plus metformin XR 1500 mg once daily (n = 138), or metformin XR 500 mg plus metformin 1500 mg (n = 144), for a total of 18 weeks. At the end of the study length, the change in A_{1c} for the saxagliptin plus metformin group was a decrease of 0.88% versus a decrease of 0.35% in the metformin only group. The difference between the two groups was a decrease of 0.52% ($P < 0.0001$, 95% CI −0.73 to −0.31). Fasting and post prandial glucose reductions ($P = 0.0013$, 95% CI −37.6 to −9.28, $P = 0.003$, 95% CI −21.86 to −4.5 respectively) and total number of patients achieving $A_{1c} < 7\%$ ($P = 0.0459$, 95% CI 0.2 to 22) were significantly greater in the saxagliptin plus metformin XR group when compared to the metformin increased dose group. Safety and tolerability with regard to adverse effects and patient reported outcomes were similar between both groups.

The combination saxagliptin plus metformin has also been studied in an Asian population with type 2 diabetes.[40] A phase 3, multi-center, randomized, parallel-group, double-blind, placebo controlled trial evaluated the safety and efficacy of saxagliptin plus metformin versus metformin alone. This study evaluated change in A_{1c} after 24 weeks in Asian patients with type 2 diabetes who had inadequate glycemic control on metformin alone. Open label metformin was prescribed at dosages of 1500, 2000, 2500, or 3000 mg/day with either saxagliptin 5 mg (n = 283) or placebo (n = 287) daily. At 24 weeks, decrease in A_{1c} was greater in the saxagliptin plus metformin group versus the metformin monotherapy group, with change in A_{1c} of −0.42% ($P < 0.0001$, 95% CI −0.55, −0.29). These results, in addition to the safety and tolerability profiles, reflect similar findings compared to the Western population.

Pharmacoeconomic analysis

Cost of new medications in comparison with standard treatment is frequently a concern for both patients and prescribers. Few analyses are available. In Germany, a cost-effectiveness evaluation was completed investigating the use of fixed dose combination saxagliptin plus metformin versus glipizide plus metformin.[41] The trial found that saxagliptin plus metformin was associated with a lower incidence of symptomatic and severe hypoglycemic events and caused more weight loss than glipizide plus metformin. The differences resulted in an incremental benefit of 0.12 quality adjusted life years in favor of saxagliptin plus metformin over saxagliptin plus glipizide. The authors concluded that these improved outcomes with saxagliptin would make the drug an acceptable cost alternative to patients in Germany. In Brazil, a cost-utility ratio simulation model was created to estimate the cost of combination saxagliptin and metformin compared with rosiglitazone or pioglitazone with metformin.[42] Saxagliptin plus metformin showed cost savings and greater effectiveness over a projected three year time span.[42] Similar analyses have not been completed in the United States or Asia, or other countries in Europe and South America at this time.[41]

Patient Preference

Patient compliance, adherence, and persistence in maintaining therapeutic treatment is a complex triad that includes patient and treatment regimen factors that may ultimately provide a barrier to medication adherence.[4] A standard measure of patient adherence to medication is calculated as patients achieving greater than 80% of their medication prescribed.[4] An average estimate of patient non-adherence is 32.5% in patients with diabetes, despite data to indicate treatment reduces long term microvascular and macrovascular complications.[4] Few clinical trials measured patient satisfaction and adherence to the combination saxagliptin plus metformin XR. Overall, patients receiving saxagliptin 5 mg/metformin 1500 mg XR showed improved treatment satisfaction compared with patients taking a higher dose of metformin XR (95% CI −0.03 to 4.47).[18] The patient burden score, efficacy subscale, and symptom score in this same population also showed greater improvement in the saxagliptin 5 mg/metformin 1500 mg XR group versus the higher dose metformin XR group (95% CI: −0.7 to 2.9, 0.7 to 9.5, −2.5 to 3.1, respectively).[18] Additionally, this population did report a level of bother in relation to abdominal gas or bloating, or diarrhea, to be greater in the saxagliptin/metformin group versus the uptitrated metformin group, described as a difference of 6.6% (95% CI −5.5 to 18.4%).[18]

Place in Therapy

As discussed above, the addition of saxagliptin to metformin therapy provides further decrease in A_{1c} from baseline, and allows for more patients to achieve A_{1c} goal than those on monotherapy with either agent alone.[36–38] Furthermore, patients who received this combination therapy had similar adverse effect profiles and discontinuation rates secondary to adverse effects as patients receiving monotherapy with metformin or saxagliptin alone.[36,37] Thus, the combination of saxagliptin and metformin provides a treatment modality using agents of differing mechanisms of action, and more attractive adverse effect profiles than other pharmacotherapies used to treat hyperglycemia in type 2 diabetes.[36,37]

Conclusions

In conclusion, the combination of saxagliptin plus metformin for the treatment of type 2 diabetes offers an oral treatment regimen that is effective and well tolerated. This agent provides an attractive combination to utilize metformin, recommended as the first line treatment, with a DPP-4 inhibitor when tailoring patient specific therapies in the treatment of type 2 diabetes.

Author Contributions

Wrote the first draft of the manuscript: MM, MK, BT. Contributed to the writing of the manuscript: MM, MK, BT. Agree with manuscript results and conclusions: MM, MK, BT. Jointly developed the structure and arguments for the paper: MM, MK, BT. Made critical revisions and approved final version: MM, MK, BT. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

References

1. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States,* 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
2. Ismail-Beigi F. Glycemic management of type 2 diabetes mellitus. *N Engl J Med*. 2012;366(14):1319–27.
3. Gallwitz B. New treatments in the management of type 2 diabetes: a critical appraisal of saxagliptin. *Diabetes Metab Syndr Obes*. 2010;10(3):117–24.
4. Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. *Int J Clin Pract*. Mar 2011;65(3):314–22.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;6(35):1364–79.
6. American Diabetes Association. Diagnosis and Classification. *Diabetes Care*. 2012;35(Suppl 1):S64–71.
7. Goldfine AB, Kulkarni RN. Modulation of β-cell function: a translational journey from the bench to the bedside. *Diabetes Obes Metab*. 2012;14 Suppl 3:152–60.
8. Leroith D. Pathophysiology of the metabolic syndrome: implications for the cardiometabolic risk associated with type 2 diabetes. *Am J Med Sci*. 2012;343(1):13–6.
9. DeFronzo RA. Overview of newer agents: where treatment is going. *Am J Med*. 2010;123(3):S38–48.
10. Wajchenberg BL. β-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev*. 2007;28(2):187–218.
11. Tahrani AA, Bailey C, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. *Lancet*. 2011;378(9786):182–97.
12. Nauck MA. Unraveling the science of incretin biology. *Am J Med*. 2009;122(Suppl 6):S3–10.
13. Hamet P. What matters in ADVANCE and ADVANCE-ON. *Diabetes Obes Metab*. 2012;14 Suppl 1:20–9.
14. Laakso M, Cederberg H. Glucose control in diabetes: which target level to aim for? *J Intern Med*. 2012;272(1):1–12.
15. Dricker D. DPP-4 inhibitors. *Diabetes Care*. 2011;34 Suppl 2:S276–8.
16. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–89.
17. Mahmood K, Naeem M, Rahimnajjad NA. Metformin: the hidden chronicles of a magic drug. *Eur J Intern Med*. 2013;24(1):20–6.
18. Fonseca V, Zhu T, Karyekar C, Hirshberg B. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. *Diabetes Obes Metab*. 2012;14(4):365–71.
19. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patinets with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52 week randomized controlled trial. *Int J Clin Pract*. 2010;64(12):1619–31.
20. Boulton DW, Smith CH, Li L, Huang J, Tang A, LaCreta FP. Bioequivalence of saxagliptin/metformin extended-release (XR) fixed-dose combination tablets and single-component saxagliptin and metformin XR tablets in healthy adult subjects. *Clin Drug Investig*. 2011;31(9):619–30.
21. Bristol-Myers Squibb. Kombiglyze™ package insert. Princeton, NJ; 2012.
22. Bristol-Myers Squibb. Onglyza® package insert. Princeton, NJ; 2011.

23. Shubrook J, Colucci R, Guo A, Schwartz F. Saxagliptin: A selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. *Clin Med Insights Endocrinol Diabetes*. 2011;4:1–12.
24. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131–57.
25. Derosa G, Maffioli P. Patient considerations and clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes*. 2011;4:263–71.
26. Bristol-Myers Squibb. Glucophage® and Glucophage® XR package insert. Princeton NJ; 2009.
27. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes*. 2000; 49(12):2063–9.
28. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108(8):1167–74.
29. Musi N, Hirshman MF, Nygren J, et al. Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. *Diabetes*. 2002;51(7):2074–81.
30. Zang M, Zuccollo A, Hou X, et al. AMP-activated protein kinase is required for the lipid-lowering effect of metformin in insulin-resistant human HepG2 cells. *J Biol Chem*. 2004;279(46):47898–905.
31. Manucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care*. 2001;24(3):489–94.
32. Migoya EM, Bergeron R, Miller JL, et al. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. *Clin Pharmacol Ther*. 2010;88(6):801–8.
33. Rojas LBA, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol Metab Syndr*. 2013;5(1):6.
34. Patel CG, Kornhauser D, Vachharajani N, et al. Saxagliptin, a potent, selective inhibitor of DPP-4, does not alter the pharmacokinetics of three oral antidiabetic drugs (metformin, glyburide or pioglitazone) in healthy subjects. *Diabetes Obes Metab*. 2011;13(7):604–14.
35. Bristol Myers Squibb. Bioequivalence study of fixed dose combination of 5 mg saxagliptin and 500 mg metformin XR tablet relative to 5 mg saxagliptin tablet and 500 mg metformin XR tablet. http://clinicaltrials.gov/ct2/show/NCT01192139?term=saxagliptin+AND+metformin&rank=4. NCT01192139.
36. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab*. 2009;11(6):611–22.
37. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R. Initial combination therapy with saxagliptin and metformin provides sustained glycemic control and is well tolerated for up to 76 weeks. *Diabetes Obes Metab*. 2011;13(6):567–76.
38. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009;32(9):1649–55.
39. Karyekar C, Donovan M, Allen E, Fleming D, Ravichandran S, Chen R. Efficacy and safety of saxagliptin combination therapy in US patients with type 2 diabetes. *Postgrad Med*. 2011;123(4):63–70.
40. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of Bra randomized controlled trial. *Diabetes Res Clin Prac*. 2011;94:217–24.
41. Erhardt W, Bergenheim K, Duprat-Lomon I, McEwan P. Cost effectiveness of saxagliptin and metformin versus sulfonylurea and metformin in the treatment of type 2 diabetes mellitus in Germany: a Cardiff diabetes model analysis. *Clin Drug Investig*. 2012;32(3):189–202.
42. Nita ME, Eliaschewitz FG, Ribeiro E, et al. Cost-effectiveness and budget impact of saxagliptine as additional therapy to metformin for the treatment of diabetes mellitus type 2 in the Brazilian private health system. *Rev Assoc Med Bras*. 2012;58(3):294–301.