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REVIEW

Saxagliptin a New Second Line Therapy After metformin for the Treatment of Type 2 Diabetes

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Abstract: Type 2 diabetes mellitus (T2DM) is a major public health problem that affects an increasingly larger number of individuals worldwide. Metformin, unless contraindicated, is the recommended first line pharmacological treatment as it can achieve good glycemic control without weight gain or hypoglycemia and with evidence for cardioprotection. T2DM is a progressive disease, and consequently further therapeutic agents are needed in order to maintain good glycemic control and prevent long-term complications. These drugs are commonly associated with undesirable side effects such as weight gain and hypoglycaemia. Moreover, none have been proven to slow or prevent the progression of T2DM (which is mainly due to progressive β-cell failure). As a result, new agents based on newer therapeutic targets are needed. Incretin based therapy is the latest addition to the currently available anti diabetes treatment and includes two groups of agents: glucagon-like peptide-1 (GLP-1) analogues/mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents act either by supplying exogenous GLP-1 (GLP-1 analogues/mimetics) or by preventing the degradation of endogenous GLP-1 (DPP-4 inhibitors). GLP-1 is a gut hormone that is mainly secreted secondary to oral glucose ingestion and results in glucose-dependent insulin secretion and glucose-dependant glucagon suppression which in turn improve fasting and post-prandial glucose levels. GLP-1 is rapidly inactivated by the DPP-4 enzyme. There are several DPP-4 inhibitors currently available, including sitagliptin, vildagliptin and saxagliptin while others are in development. Due to their mechanism of action, DPP-4 inhibitors are associated with low risk of hypoglycemia and are weight neutral. As a result, they are attractive agents particularly in combination with metformin therapy. In this article we will examine the potential use of saxagliptin as an add-on therapy to metformin in patients with T2DM.

Keywords: Dipeptidyl-Peptidase 4 inhibitors, saxagliptin, incretins, GLP-1, hypoglycemic agents, metformin, type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated worldwide prevalence of 6% (246 million people) in 2007; forecasted to rise to 7.3% (380 million) by 2025.[1] The health, social, and economic burden of T2DM is great;[2–4] consequently, T2DM presents a major challenge to healthcare systems around the world.

T2DM is a complex disorder in which the interaction between environmental and genetic factors results in the development of insulin resistance (IR) and pancreatic β-cell dysfunction.[5,6] While not all patients with T2DM have IR, the development of IR precedes the onset of T2DM by many years[5,7] and is influenced by multiple factors including puberty, ageing, pregnancy, physical activity and oral intake.[8–12] Overweight/obesity is the single most important contributor to IR.[12]

Despite obesity being the single most important contributor to IR, most obese insulin-resistant individuals do not develop T2DM[6,12,13] because their β-cells are capable of producing significantly elevated levels of insulin to maintain glycemic control.[12,14–17] Hence, the failure of β-cells to secrete sufficient insulin to overcome IR (i.e. β-cell dysfunction) is the crucial step in the development and progression of T2DM.[5,6,12,14] In addition to β-cell dysfunction, patients with T2DM have pancreatic α-cell dysfunction manifesting as elevated (or non-suppressed) glucagon secretion in the presence of hyperglycemia.[18]

Based on our current understanding of the pathophysiology of T2DM, multiple pharmacological and non-pharmacological interventions have been developed over the past five decades with the aim of improving glycemic control and hopefully slowing disease progression. To an extent, there has been some disappointment in that most of the observed initial improvements in glycemic control are not sustained because of the progressive nature of the disease.[19,20] These treatments may also have undesired side effects, such as hypoglycemia, weight gain, gastrointestinal symptoms and peripheral oedema, in addition to variable effects on β-cell function and decline.[20,21]

Metformin is a well established first-line pharmacological treatment for patients with T2DM.[22,23] However, due to the progressive nature of the disease, most patients will require the addition of further anti-diabetes agents or insulin therapy.[19,24] Hence, interventions which can slow and/or reverse β-cell decline, which result in weight loss (or at least cause no weight gain) and which have a low risk of hypoglycemia, would be expected to play an important role in the management of patients with T2DM.

Incretin-based therapies are the latest class of anti-diabetes agents to become available. Incretin-based therapy consist of incretin analogues/mimetics (exenatide and liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin). These new agents might address some of the above-mentioned shortfalls of current treatments. There are several other incretin-based therapies and new classes of anti diabetes agents in development with the potential to address some of the disadvantages of currently available treatments.[25]

In this article we will discuss the role of saxagliptin in combination with metformin as a treatment strategy in patients with T2DM. Other DPP-4 inhibitors are also available in combination tablets with metformin.[26,27]

The Incretins

The incretin effect was first described following the observation that insulin responses to oral glucose exceed those measured after intravenous administration of equivalent amounts of glucose (Fig. 1, adapted from).[28,29] This effect is responsible for 50%–70% of the insulin response to a meal in healthy individuals.[30]

Two incretins, GIP (glucose insulinotropic polypeptide, initially called gastric inhibitory polypeptide) and GLP-1 (glucagon-like peptide 1) have been described and extensively studied. They are secreted from the gastrointestinal tract during food intake and bind to specific G protein-coupled receptors that are found in the pancreas, stomach, skeletal muscle, heart, lung and brain.[31,32] This wide distribution of their receptor might explain the variety of effects that incretins have.

Glucose Insulinotropic Peptide (GIP)

GIP was the first incretin to be described. It is a single 42 amino acid peptide derived from a 153 amino acid precursor, whose gene is located on chromosome 17.[33,34] It is secreted in a single bioactive from the K-cells in the duodenum and jejunum in response to the ingestion of carbohydrates and/or lipids.[33–35]

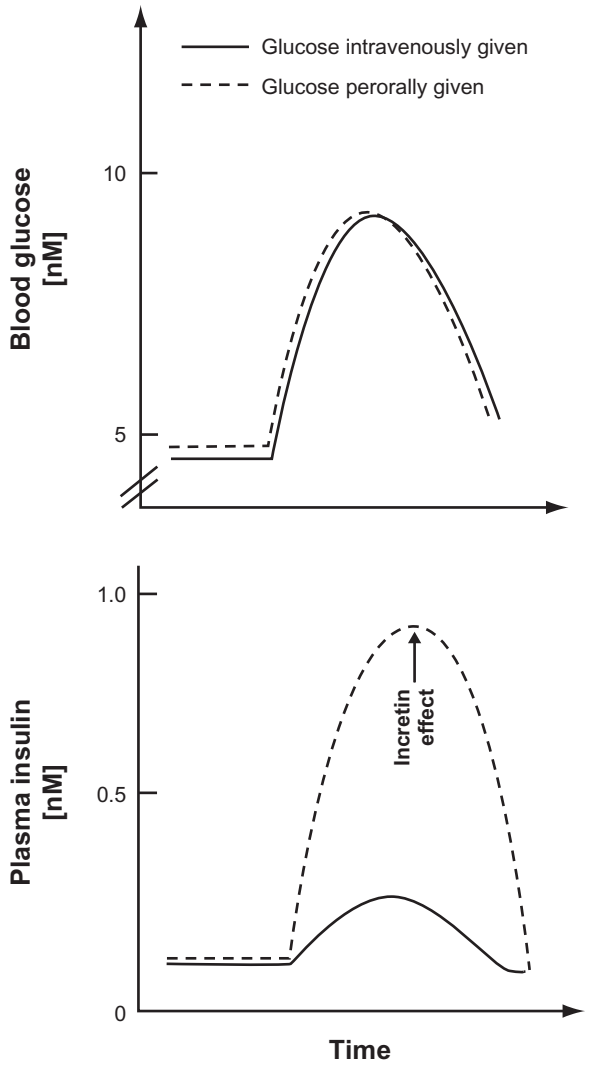

Figure 1. The incretin effect. Note the difference in plasma insulin following oral and intravenous glucose. Adapted from Verspohl 2009.

GIP results in glucose-dependent insulin secretion in humans.[34–36] In addition, it plays a role in fat metabolism in the adipocytes and has a proliferative effect on the β-cells.[34,37,38]

Unlike glucagon-like peptide-1 (GLP-1), GIP has no effect on the α-cells that secrete glucagon and has no impact on food intake, satiety, gastric emptying or body weight.[34,39] In T2DM, GIP levels are either normal or increased, while GLP-1 levels are usually reduced which made GLP-1 a more attractive target for therapeutic development.[40–42]

GLP-1

This was the second incretin to be discovered. GLP-1 is cleaved from pro-glucagon (the gene is situated on chromosome 2) and secreted from the L-cells in the distal ileum and colon.[34,35] GLP-1 and GIP contribute and potentiate glucose-dependent insulin secretion in an additive manner, but GLP-1 appears to be responsible for the majority of the incretin effect on the β-cell.[31,35] Despite the distal location of the L cells, GLP-1 is secreted within minutes following oral intake which suggests that neural and endocrine factors rather than direct stimulation are involved.[34,35] These factors are not well understood in humans, but animal models suggest a role for taste receptors and vagal stimulation.[34,35,43,44]

GLP-1 has a number of functions including: stimulation of glucose-dependent insulin secretion, glucose-dependent glucagon suppression, slowing of gastric emptying, reduction of food intake and possibly improved insulin sensitivity.[30,31,45] In addition, GLP-1 increases insulin gene transcription and all steps of insulin biosynthesis.[40,41] Animal studies showed that GLP-1 increases β-cell mass, maintains β-cell efficiency and reduces β-cell apoptosis.[45,46]

Although GLP-1 levels are reduced in patients with T2DM, their response to exogenous GLP-1 remains intact.[47] Compared to normoglycemic subjects without T2DM, patients with T2DM have a blunted GLP-1 secretory response in relation to meal ingestion, while patients with impaired glucose tolerance have GLP-1 secretory rates intermediate between the subjects with and without T2DM.[48] A continuous 6 hours intravenous infusion of GLP-1 in the fasting state, leading to GLP-1 levels 2–3 times higher than normally seen after meals, resulted in lowering of glucose (without any hypoglycaemic events), glucagon and NEFA levels with increases in insulin secretion in patients with poorly controlled T2DM.[49] Exogenous subcutaneous GLP-1 administration was also shown to have a significant postprandial blood glucose lowering effect when administered subcutaneously before meals in overweight patients with T2DM.[50]

Inactivation of incretin hormones

GIP and GLP-1 are rapidly degraded by the enzyme DPP-4[35] which cleaves the active peptide at position 2 alanine (N-terminal) resulting in inactive peptide.[34]

DPPs are a subclass of the serine protease family and include DPP-1 to 4, fibroblast activation protein, DPP-8 and DPP-9. DPP-4 is the only DPP to have

been well characterized and to have had its natural substrate identified. DPP-4 is widely expressed in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine and lymphocytes.[34] It is also found in the endothelial cells of the blood vessels that drain the intestinal mucosa where the L-cells are situated.[34,51] This suggests that the majority of GLP-1 is inactivated almost immediately following secretion. This rapid inactivation of GLP-1 and GIP contributes to a half-life of <2 min and 5–7 minutes respectively.[34,35,52,53] The short half life limits the therapeutic potential of incretins. To overcome this problem, inhibitors of DPP-4 were developed and modifications of the amino acids at the N-terminus of GLP-1 and GIP (which is susceptible to DPP-4 cleavage) were performed (incretin mimetics/analogues) resulting in DPP-4 resistance with variable receptor activation and biological activity.[32] Further details regarding the biochemistry and development of DDP-4 inhibitors can be found in.[54]

Mechanism of Action, Metabolism and Pharmacokinetics

Metformin

Biguanides can be traced from the use of *Galega officinalis* (goat's-rue or French lilac) as a treatment for diabetes in medieval Europe.[55] Metformin (Dimethylbiguanide), the only available biguanide, was introduced in the 1950s and remains the first line drug therapy for patients with T2DM.[22,23,55] It acts by decreasing hepatic glucose output and and decreasing fatty acid oxidation.[55] In hepatocytes, metformin activates AMPK (AMP-activated protein kinase), a major regulator of lipid and glucose metabolism, which results in inhibition of lipogenesis, increased fatty acid oxidation and inhibition of hepatocyte glucose production.[56] AMPK is also present in muscle cells and its activation might be responsible for the observed decresed peripheral insulin resistance and increased peripheral insulin mediated glucose disposal.[55,56] In addition, metformin increases GLP-1 levels by inhibiting DPP-4 and/or increasing GLP-1 production, which could explain its weight neutral effect, and increases glucose turnover by interfering with lactate metabolism.[57–60] Metformin is not metabolized, little is protein-bound and it is rapidly cleared unchanged in the urine by glomerular filtration and tubular secretion.[61] Metformin (500–1000 mg) has a bioavailability of 50%–60%, a t_{max} 3–8 hours, a plasma half life of 1.5–4.9 hours and an elimination $t_{1/2}$ of 6 hours.[55,61] Gender has no effect on metformin pharmacokinetics; age, however, seems to have an impact (decreased clearance, prolonged half life and increased C_{max}) mainly due to reduction in renal function in elderly subjects.[62] The advantages of metformin are a very low risk of hypoglycemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality.[63,64]

Saxagliptin

Saxagliptin is a selective, durable but reversible inhibitor of the DPP-4 enzyme. Preclinical studies suggest that saxagliptin shows a high sensitivity for DPP-4 and a low affinity for DPP-8 and DPP-9.[65] Saxagliptin demonstrates greater specificity for DPP-4 than for either the DPP-8 or DPP-9 enzymes (400-fold and 75-fold, respectively).[66] The active metabolite of saxagliptin (BMS-510849) is two-fold less potent than the parent. Both saxagliptin and its metabolite are highly selective (>4000-fold) for inhibition of DPP-4 compared with a range of other proteases.[67] Systemic exposure to saxagliptin has been shown to be dose proportional, and pharmacokinetic parameters to be similar in patients with T2DM and in healthy individuals. Saxagliptin inhibits DPP-4 at doses between 2.5 and 400 mg, with doses greater than 150 mg providing the same maximal inhibition.[68] The impact of age and/or gender was assessed in a study of 56 healthy subjects. It was shown that saxagliptin exposure was slightly increased (less than two-fold) in elderly individuals (aged ≥65 years) following a single oral 10 mg dose, compared with younger individuals (aged 18–40 years). In the same study, only small differences in saxagliptin pharmacokinetics were observed between healthy male and female subjects. The authors of the study concluded that no dosage adjustment for saxagliptin was necessary on the basis of age or gender.[69]

Saxagliptin in combination with metformin

The effect of co-administration of metformin 1000 mg and saxagliptin 100 mg on the single-dose pharmacokinetics of each individual drug was investigated in 16

healthy males. Metformin co-administration lowered saxagliptin C-max (geometric mean 0.79; 90% confidence intervals [0.71, 0.87]) although the authors of the study concluded that this was unlikely to be of clinical consequence. Metformin did not affect the overall exposure to saxagliptin or its metabolite, and saxagliptin did not alter the overall exposure to metformin.[70]

Saxagliptin and metformin have synergetic mechanisms of action. While metformin mainly acts by reducing hepatic glucose output and increasing glucose uptake by muscle, saxagliptin increases insulin and reduces glucagon secretion in a glucose dependent manner by inhibiting DPP-4 and increases endogenous GLP-1 levels. Furthermore, metformin has been shown to increase GLP-1 levels.[58,60] The lack of clinically significant pharmacokinetic interactions, in addition to their synergetic mechanisms of actions, makes the addition of saxagliptin to metformin a logical choice in the management of patients with T2DM.

Efficacy

Metformin lowers fasting plasma glucose concentrations and improves HbA1c levels in patients with T2DM regardless of age, ethnic group, baseline body-mass index or duration of diabetes when used as monotherapy or in combination with other oral antidiabetes drugs.[55]

Saxagliptin has been shown to reduce FPG, PPG and HbA1c when used alone or in combination with other OAD.[70] In addition, Saxagliptin has been shown to improve surrogate markers of β-cell function in patients with T2DM.[67] The efficacy of saxagliptin in patients with T2DM from published RCTs (randomised controlled trials), including saxagliptin monotherapy and combination therapy with sulphonylureas or metformin is summarized in Table 1.[71–75] Saxagliptin has also been examined in combination with TZD in a study of 565 patients with inadequate glycemic control (HbA_{1c} 7.0%–10.5%). Patients were randomized to receive add-on therapy with saxagliptin (2.5 mg or 5.0 mg) or placebo once daily, in addition to either pioglitazone (30 mg or 45 mg) or rosiglitazone (4 mg or 8 mg) for 24 weeks.[76] At week 24, saxagliptin (2.5 mg and 5.0 mg) add-on treatment provided significant adjusted-mean reductions in HbA1c from baseline (–0.66% and –0.94%, respectively) compared with placebo (–0.30%; both $P < 0.001$). Significant reductions were also observed with saxagliptin (2.5 mg and 5 mg) for FPG (–14.3 mg/dL (–0.8 mmol/l) and –17.3 mg/dL (–1.0), respectively) compared with placebo (–2.8 mg/dL (–0.2 mmol/l); both $P < 0.01$), and for PPG AUC (–7849 mg · min/dL (–436 mmol · min/l) and –9269 mg · min/dL (–514 mmol · min/l), respectively) compared with placebo (–2690 mg·min/dL (–149 mmol · min/l); both $P < 0.0001$). Finally, a significantly ($P < 0.01$) greater proportion of patients reached target HbA1c levels (<7.0%) in the saxagliptin groups (both 42%) compared with the placebo group (26%).[76]

Saxagliptin in combination with metformin

Saxagliptin co-administration with metformin has been studied either as an add-on or as a first line combination therapy (Table 1). Initial combination therapy with saxagliptin plus metformin was investigated in drug-naïve patients with inadequately controlled T2DM (HbA_{1c}, 8%–12%; $n = 1306$). In this phase 3 trial, over 1,300 treatment-naive patients with T2DM found that the combination of saxagliptin (5–10 mg daily) with metformin (up to 2 g daily) led to significantly greater improvements in HbA1c than either drug alone over a period of 24 weeks.[73] The HbA1c was lowered by 2.5% in both combination groups, compared with 1.7% in the saxagliptin monotherapy group and 2.0% in the metformin monotherapy group ($P < 0.0001$ for combination vs. each monotherapy).[73] FPG was also lower in the groups receiving combination therapy (compared with baseline –60 mg/dl (–3.3 mmol/l), –62 mg/dl (–3.4 mmol/l), –31 mg/dl (–1.7 mmol/l), –47 mg/dl (–2.6 mmol/l) for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin respectively, $P < 0.0001$ for each combination vs. saxagliptin monotherapy and $P \leq 0.002$ for each combination vs. metformin monotherapy).[73] PPG was also lower in the combination therapy group after 24 weeks of treatment. The 2-hour PPG levels were reduced by –138, –137, –106, –97 mg/dl (–7.7, –7.6, –5.9, –5.4 mmol/l) in patients taking saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg only and metformin only respectively ($P \leq 0.0002$ for

Table 1. Summary of Randomised Controlled Trials looking at the effect of saxagliptin on glycaemic parameters and weight in comparison with placebo or other oral antidiabetes drugs.

Study	Duration (weeks)	Number of patients	Design	Baseline HbA_{1c} (mean ± SD)	HbA_{1c} (mean change from baseline ± SE or mean change (95% CI))
Rosenstock et al[74] (low-dose cohort)	12	338	Arm 1: saxagliptin 2.5	7.7 ± 0.97	–0.72 (–0.97 to –0.48)
			Arm 2: saxagliptin 5	7.9 ± 1.09	–0.90 (–1.17 to –0.63)
			Arm 3: saxagliptin 10	8.0 ± 1.14	–0.81 (–1.03 to –0.58)
			Arm 4: saxagliptin 20	7.9 ± 0.99	–0.74 (–0.98 to –0.50)
			Arm 5: saxagliptin 40	7.8 ± 1.00	–0.80 (–1.04 to –0.56)
			Arm 6: placebo	8.0 ± 0.98	–0.27 (–0.49 to –0.05) ($P < 0.007$ for arms 1 to 5 vs. arm 6)
Rosenstock et al[74] (high-dose cohort)	6	85	Arm 1: saxagliptin 100	7.8 ± 1.01	–1.09 (–1.26 to –0.92)
			Arm 2: placebo	7.5 ± 1.05	–0.36 (–0.55 to –0.17)
Chacra et al[71]	24	768	Arm 1: saxagliptin 2.5 + glyburide 7.5	8.4 ± 0.9	–0.54[a]
			Arm 2: saxagliptin 5 + glyburide 7.5	8.5 ± 0.9	–0.64[a]
			Arm 3: glyburide 10 + placebo	8.4 ± 0.9	+0.08[a] ($P < 0.0001$ for arms 1 and 2 vs. arm 3)
Jadzinsky et al[73]	24	1306	Arm 1: saxagliptin 5 + metformin up to 2000	9.4 ± 1.2	–2.5[a]
			Arm 2: saxagliptin 10 + metformin up to 2000	9.5 ± 1.2	–2.5[a]
			Arm 3: saxagliptin 10 + placebo	9.6 ± 1.3	–1.7[a]
			Arm 4: placebo + metformin up to 2000	9.4 ± 1.3	–2.0[a] ($P < 0.0001$ for arm 1 and 2 vs. arm 3, $P < 0.0001$ for arm 1 and 2 vs. arm 4)
DeFronzo et al[72]	24	743	Arm 1: metformin + saxagliptin 2.5	8.1 ± 1.0	–0.59 ± 0.07
			Arm 2: metformin + saxagliptin 5	8.1 ± 0.8	–0.69 ± 0.07
			Arm 3: metformin + saxagliptin 10	8.0 ± 1.0	–0.58 ± 0.07
			Arm 4: metformin + placebo	8.1 ± 0.9	+0.13 ± 0.07
Rosenstock et al[75] (main treatment cohort)	24	401	Arm 1: saxagliptin 2.5	7.9 ± 0.9	Arm 1: –0.43[a]

Baseline FPG (mean ± SD)	FPG change from baseline (mean ± SE or mean (95% CI))	PPG change from baseline (mean ± SE or mean change (95% CI))	Baseline BMI (mean ± SD)	Weight change from baseline (mean change (95% CI))	Confirmed hypoglycaemia[b] patients: number (%)
8.6 ± 2.2	–0.6 (–1.1 to –0.1)	–1.4 (–2.1 to –0.6)	30.8 ± 3.73	–0.94 (–1.64, –0.23)	None
9.4 ± 2.8	–1.2 (–1.7 to –0.7)	–2.0 (–2.8 to –1.1)	30.8 ± 4.21	–0.23 (–1.07, +0.60)	None
9.4 ± 2.5	–0.9 (–1.3 to –0.4)	–2.3 (–2.9 to –1.6)	31.0 ± 4.03	–1.28 (–2.09, –0.47)	None
9.6 ± 2.7	–0.8 (–1.2 to –0.3)	–1.5 (–2.3 to –0.8)	29.7 ± 3.63	–0.11 (–0.81, 0.59)	None
8.8 ± 2.4	–0.9 (–1.4 to –0.4)	–1.9 (–2.6 to –1.1)	29.8 ± 4.29	0.51 (–0.41, 1.42)	None
9.2 ± 2.4	+0.2 (–0.3 to +0.6)	–0.1 (–0.7 to +0.6)	31.3 ± 4.46	–1.03 (–1.80, –0.27)	None
8.5 ± 2.0	–1.5 (–1.8, –1.1)	–2.5 ± 0.3	31.3 ± 3.88	–0.20 (–0.85, +0.45)	2 (4.5)
8.0 ± 1.9	–0.2 (–0.6, +0.2)	–1.0 ± 0.3	31.2 ± 4.06	–0.85 (–1.37, –0.33)	0
9.4 ± 2.3	–0.4[a]	–2[a]	29.1 ± 4.5	+0.7	6 (2.4)
9.7 ± 2.5	–0.5[a]	–2[a]	29.2 ± 4.6	+0.8	2 (0.8)
9.7 ± 2.4	+0.04[a]	+0.4[a]	28.8 ± 4.7	+0.3	2 (0.7)
	(P = 0.0218 for arm 1 vs. arm 3 and 0.0002 for arm 2 vs. arm 3)	(P < 0.0001 for arm 1 and 2 vs. arm 3)		(P = 0.0381 arm 1 vs. arm 3 and P = 0.01202 arm 2 vs. arm 3)	(P = ns for arm 1 and 2 vs. arm 3)
11.1 ± 3.1	–3.3[a]	–7.7[a]	29.9 ± 5.3	–1.8	0 (0)
11.3 ± 3.3	–3.4[a]	–7.6[a]	30.3 ± 5.0	–1.4	2 (0.6)
11.2 ± 3.0	–1.7[a]	–5.9[a]	30.2 ± 4.9	–1.1	0 (0)
11.0 ± 3.3	–2.6[a]	–5.4[a]	30.2 ± 4.9	–1.6	1 (0.3)
	(P < 0.0001 for arm 1 and 2 vs. arm 3, P = 0.0002 for am 1 vs. arm 4, P < 0.0001 for arm 2 vs. arm 4)	(P = 0.0001 for arm 1 vs. arm 3, P = 0.0002 arm 2 vs. arm 3, P < 0.0001 for arm 1, 2 and 3 vs. arm 4)			
9.7 ± 2.4	–0.8 ± 0.1	–3.4 ± 0.3	31.7 ± 5.2	–1.43	1 (0.5)
10 ± 2.6	–1.2 ± 0.1	–3.2 ± 0.3	31.2 ± 4.7	–0.87	1 (0.5)
9.8 ± 2.8	–1.1 ± 0.1	–2.7 ± 0.3	31.1 ± 4.8	–0.53	1 (0.6)
9.7 ± 2.4	–0.1 ± 0.1 (P ≤ 0.0001 for arms 1 to 3 vs. arm 4)	–1.0 ± 0.3	31.6 ± 4.8	–0.92	1 (0.6)
9.9 ± 2.3	–0.8[a]	–2.5	31.9 ± 4.8	–1.2	None

(*Continued*)

Table 1. (*Continued*)

Study	Duration (weeks)	Number of patients	Design	Baseline HbA_{1c} (mean ± SD)	HbA_{1c} (mean change from baseline ± SE or mean change (95% CI))
			Arm 2: saxagliptin 5 Arm 3: saxagliptin 10 Arm 4: placebo	8.0 ± 1.1 7.8 ± 0.9 7.9 ± 0.9	Arm 2: –0.46[a] Arm 3: –0.54[a] Arm 4: +0.19[a] ($P < 0.0001$ for arms 1 to 3 vs. arm 4)
Rosenstock et al[74] (open label cohort)	24	68	Saxagliptin 10	10.7 ± 0.8	–1.87 ± 0.18
Hollander 2009[76]	24	565	Pioglitazone (30 or 45) or rosiglitazone (4 or 8) stable dose together with: Arm 1: saxagliptin 2.5 Arm 2: saxagliptin 5 Arm 3: placebo	8.3 ± 1.1 8.4 ± 1.1 8.2 ± 1.1	–0.7[a] –0.9[a] –0.3[a] ($P = 0.0007$ for arm 1 vs arm 3, $P < 0.0001$ for arm 2 vs arm 3)

combination vs. either monotherapy). The effects were noticed as early as after 4 weeks of treatment.[73] Saxagliptin (5 mg and 10 mg) initial combination therapy with metformin provided significant increases surrogate markers of β-cell function (HOMA-2β, 33% and 38%, respectively), compared with saxagliptin 10 mg alone (HOMA-2β,18.2%) or metformin alone (HOMA-2β, 22.6%).[77]

The addition of saxagliptin to patients with inadequate glycemic control already taking metformin (1.5–2.5 g daily) was examined in a 24-week study of 743 patients with T2DM.[72] In this randomized, double-blind, placebo-controlled trial saxagliptin (2.5, 5, or 10 mg once daily) was compared to placebo. Saxagliptin (2.5, 5, and 10 mg) plus metformin demonstrated statistically significant adjusted mean decreases from baseline to compared to placebo in HBA1c (–0.59, –0.69, and –0.58 vs. +0.13%; all $P < 0.0001$), FPG (–14.31, –22.03, and –20.50 vs. +1.24 mg/dl (–0.8, –1.2 and –1.2 vs. +0.4 mmol/l); all $P < 0.0001$), and PPG AUC (–8,891, –9,586 and –8,137 vs. –3,291 mg.min/dl (–494, –533 and –452 vs. –183 mmol·min/l); all $P < 0.0001$). Saxagliptin also improved surrogate markers of β-cell function (as judged by postprandial c-peptide and insulin levels) in all saxagliptin treatment groups at week 24.[72] This initial improvement in glycaemic control at 24-week was sustained at 102 weeks.[78] In the extension, the placebo subtracted change from baseline HbA1c (mean (95% CI)) were –0.62 (–0.84, –0.4), –0.72 (–0.94, –0.5) and –0.52 (–0.74, –0.30) for saxagliptin 2.5, 5 and 10 mg respectively.[78] The proportion of patients who discontinued or rescued for lack of glycemic control was lower in the saxagliptin arms (58.3%, 51.8%, 56.9% and 71.5% for saxagliptin 2.5 mg, 5 mg, 10 mg and placebo respectively.[78]

Safety

Metformin

Metformin is generally well tolerated. The most common side effects (>5%) in a placebo controlled trial included (metformin vs. Placebo): diarrhoea (10% vs. 3%) and nausea and/or vomiting

Baseline FPG (mean ± SD)	FPG change from baseline (mean ± SE or mean (95% CI))	PPG change from baseline (mean ± SE or mean change (95% CI))	Baseline BMI (mean ± SD)	Weight change from baseline (mean change (95% CI))	Confirmed hypoglycaemia[b] patients: number (%)
9.5 ± 2.4	–0.5[a]	–2.4	32.2 ± 4.5	–0.1	None
9.9 ± 2.5	–0.9[a]	–3.0	31.7 ± 4.7	–0.1	None
9.5 ± 2.5	+0.3[a] ($P = 0.0002$ for arm 1 vs. baseline, $P = 0.0074$ for arm 2 vs. baseline, $P < 0.0001$ for arm 3 vs. baseline)	–0.3 ($P = 0.0007$ for arm 1 vs. baseline, $P = 0.0009$ for arm 2 vs. baseline, $P < 0.0001$ for arm 3 vs. baseline)	30.9 ± 4.3	–1.4	None
13.4 ± 2.7	–1.8 ± 0.3	–3.7 ± 0.7	31.7 ± 4.73	+0.1	None
9 ± 2.7	–0.8[a]	–3[a]	30.0 ± 5.8	+1.3	1 (0.5)
9 ± 2.5	–1.0[a]	–4[a]	29.8 ± 5.3	+1.4	0 (0)
9 ± 2.5	–0.2[a] ($P = 0.0053$ for arm 1 vs arm 3, $P < 0.0005$ for arm 2 vs arm 3)	–1[a] ($P < 0.0001$ for arm 1 and arm 2 vs. placebo)	30.3 ± 5.8	+10.9	0 (0)

Units: HbA_{1c}: %; FPG: mmol/l; PPG, mmol/l, BMI: km/m^2, weight: kg. To convert from mmol/l to mg/dl multiply by 18.[a]The SEM numerical value is not reported in the paper but the mean ± SEM is displayed graphically. All drug doses expressed in milligrams.
[b]Confirmed hypoglycaemia was defined as symptoms consistent with hypoglycaemia with a fingerstick glucose below or equal to 2.8 mmol/l.
Abbreviations: bid, twice daily, BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; ns, nonsignificant; PPG, postprandial glucose; qd, once daily; ref., reference; SE, Standard error; tds, three times per day.

(7% vs. 2%).[62] Other side-effects which were more common in metformin treated patients included abdominal pain, constipation, abdominal distension, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.[62] Renal, liver, respiratory and heart failure and the use of intravenous contrast are the main contraindications because of the fear of lactic acidosis. Lactic acidosis is extremely rare and it has not been proven that metformin causes it.[55,79] Hypoglycemia does not occur in patients receiving metformin monotherapy under usual circumstances, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or alcohol.[62]

Metformin drug interactions have been examined in several studies. A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that furosemide increased the metformin plasma C_{max} by 22% and AUC by 15%, without any significant change in metformin renal clearance.[62] On the other hand, the C-max and AUC of furosemide were 31% and 12% smaller, respectively, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance.[62] No information is available about the interaction of metformin and furosemide when co-administered chronically.[62] Nifedipine can increase metformin absorption and can lead to small increases in metformin C-max and AUC while the effect of metformin on nifedipine is minimal.[62] Drugs that are eliminated through renal tubular secretion (such as cimetidine, amilorde, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamteren, trimethoprim, vancomycin) can theoretically compete with metformin for the same tubular transport system.[62] In practice, only the interaction between metformin and cimetidine has been well described. Cimetidine increases the C-max and AUC of metformin by 60 and 40% respectively, while metformin does not affect cimetidine pharmacokinetics.[62] Due to its negligible protein binding, metformin is not expected to interact with drugs that bind tightly to plasma proteins (such as salicylates, sulphonamides, chloramhenicol and probenecid).[62]

Saxagliptin

Saxagliptin was associated with low rates of hypoglycemia, particularly when used as monotherapy or in combination with metformin or TZD.[70] In drug-naïve patients with T2DM, saxagliptin 2.5–100 mg monotherapy once daily showed a similar tolerability profile to placebo, with a very low incidence of confirmed hypoglycemia (≤50 mg/dL) in the saxagliptin treatment arms.[74,80] When given as add-on treatment in patients with inadequate glycemic control, despite monotherapy with metformin, a TZD, or a sulphonylurea, saxagliptin 2.5–10 mg did not increase the risk of hypoglycaemia.[72,76,81] The frequency of confirmed hypoglycemia is reported in Table 1.

In initial combination therapy with saxagliptin (5 mg and 10 mg) and metformin (in drug-naïve patients) there were few reported events of hypoglycemic symptoms (saxagliptin 5 mg + metformin: 3.4%; saxagliptin 10 mg + metformin: 5.0%; saxagliptin 10 mg alone: 1.5%; and metformin alone: 4.0%).[77] The addition of saxagliptin to pioglitazone or rosiglitazone all reported frequency of hypoglycemic events similar to placebo (saxagliptin 2.5 mg, 4.1%; saxagliptin 5 mg, 2.7%; placebo, 3.8%).[76] When added to glyburide, reported hypoglycemia did not differ between groups (saxagliptin+glyburide 13.3%–14.6%, vs. glyburide 10.1%, P = non-significant).[81] However, as sulphonylureas have been shown to uncouple the glucose dependence of the insulinotropic effect of GLP-1,[82] the FDA warns of the risk of hypoglycemia when saxagliptin is used together with an insulin secretagogue and recommends that the dose of secretagogue might need reducing.[83] The incidence of severe hypoglycaemia requiring third party assistance in patients receiving saxagliptin either alone or in combination with metformin or glyburide, was very low with only one case reported (in a patient taking both saxagliptin and glyburide)in six studies (Table 1).

Saxagliptin is well tolerated with the most frequently reported side effects in a monotherapy trial being (saxagliptin vs. placebo) headache (11.5% vs. 9%), upper respiratory tract infections (7.4% vs. 6%), urinary tract infections (7.1% vs. 7.5%), nasopharyngitis (6.2% vs. 7.5%) and arthralgia (6.2% vs. 3.0%).[74] When added to metformin the most frequently reported side-effects with incidence rates above 5% (all comparisons are saxagliptin 2.5 to 10 mg + metformin vs. placebo + metformin) were nasopharingytis (8.7% vs. 7.8%), headache (8% vs. 7.3%), diarrhoea (7.1% vs. 11.2%), upper respiratory tract infection (6.6% vs. 5%), influenza (6% vs. 7.3%), urinary tract infection (5.1% vs. 4.5%), back pain (4.3% vs. 6.7%), and pain in the extremities (3% vs. 5.6%). The addition of saxagliptin to metformin did not augment the gastrointestinal intolerability of metformin.[72] When added to glyburide, the most common adverse events with occurrence rates ≥5% included (all comparisons are saxagliptin + glyburide vs. glyburide): urinary tract infection (8.0% vs. 8.2%), headache (7.6% vs. 5.6%), nasopharyngitis (5.8% vs. 6.7%), upper respiratory tract infection (5.4% vs. 6.7%), back pain (5.4% vs. 4.5%), hypertension (5.0% vs. 2.2%), diarrhoea (4.8% vs. 5.2%), influenza (4.6% vs. 6.0%), and pain in the extremities (4.0% vs. 5.6%).[81]

Saxagliptin is weight neutral in monotherapy or in combination with metformin.[72–74] In combination with glyburide a small (<1 kg) but significant weight gain compared with glyburide alone was observed in parallel with improved glycemic control.[71]

Small, reversible dose-dependent reductions in absolute lymphocyte count (up to -0.38×10^3 cells/μl) which remained within the normal range have been observed, particularly in patients receiving doses above 20 mg daily, but no associated impaired immune function has been demonstrated.[73,74]

In an open label study of a single dose of saxagliptin 10 mg the systemic exposure of saxagliptin correlated with the degree of renal impairment (1.2–4.5 fold higher than that in normal renal function).[84] In patients with end-stage renal disease, a 4-hour haemodialysis session removed 23% of saxagliptin.[84] The FDA recommends using 2.5 mg daily in patients with moderate, severe or end-stage renal disease (Creatinine Clearance < 50 ml/min) and administering the dose after haemodialysis sessions.[83] The FDA also recommends that renal function should be checked prior to and regularly after starting saxagliptin.[83] A study of 18 patients with variable degrees or hepatic dysfunction (Child-Pugh classes A to C) and matched patients with normal liver function found no significant difference in pharmacokinetics and no increased incidence of adverse events for either saxagliptin (10 mg single dose) or its active metabolite in any category of hepatic impairment compared with normal liver function.[85] However, as metformin is contraincated in

patients with liver or renal failure, the use of saxagliptin in combination with metformin in these conditions will also be contraindicated.

No significant pharmacodynamic interactions were found between saxagliptin or its metabolite and simvastatin, magnesium and aluminim hydroxides plus simethicone, famotidine, omeprazole, digoxin, metformin, glyburide or pioglitazone.[67,70,86,87] Significant drug interactions were found when saxagliptin was coadministered with ketoconazole and diltiazem, therefore, dose adjustments may be required.[67,70]

Cardiovascular safety

The United Kingdom Prospective Diabetes Study showed the use of metformin to be associated with reduction in cardiovascular events that persisted even 10 year after the end of the study.[63,64] In placebo controlled trials, metformin use (1000 mg twice daily) resulted in favourable changes in lipid profile compared to placebo (LDL baseline 131.4 vs. 131.9 mg/dl, (3.4 vs. 3.4 mmol/l) study end change −5% vs. +3.2% for metformin vs. placebo).[62] Similarly, metformin produced a favourable impact on the lipid profile when compared to glyburide (LDL: baseline 136 vs. 137.5 mg/dl (3.5 vs. 3.5 mmol/l), study end change −4% vs. +3%, triglycerides: baseline 215 vs. 266 mg/dl (2.4 vs. 3 mmol/l), study end change −3% vs. +4%)

A recent review of eight randomized, double-blind, phase 2b or 3 trials totalling 3758 patient-years on saxagliptin and 1293 patient-years on comparators (placebo, metformin, glyburide) found no increased risk of cardiovascular events and suggested saxagliptin might be cardioprotective (hazard ratio for major adverse cardiovascular events defined as stroke, myocardial infarction or stroke 0.44 (95% CI: 0.24–0.82), for acute cardiovascular event 0.59 (95% CI: 0.35–1.00)).[88] Eighty-one percent of patients within the saxagliptin group had at least one cardiovascular risk factor in addition to T2DM.[88]

In summary, the use of saxagliptin in combination with metformin is well tolerated, weight neutral, with very low risk of hypoglycemia and no increase in the incidence of gastrointestinal side effects.[26,70] Although each drug seems to be safe from a cardiovascular point of view, no data is available about the cardiovascular safety of the combination. In addition, there is no long term data on the cardiovascular safety of saxagliptin.

Place in Therapy

Saxagliptin was approved by the FDA in July 2009 for the treatment of patients with T2DM as monotherapy or in combination with metformin, thiazolidinediones or sulphonylureas.[83] The use of saxagliptin with insulin is not licensed.[83] The EMEA approved the use of saxagliptin in combination with metformin, sulphonylurea or thiazolidinedione in October 2009.[89]

Metformin remains a well-established first line treatment (in addition to life style changes) in patients with T2DM due to its efficacy, long-term safety, weight neutrality and cardiovascular benefits. However, most patients with T2DM require the addition of other anti-diabetes treatments to maintain glycaemic control. At this stage, the clinician needs to make the choice between different oral and injectable treatments balancing the risks of the older well established anti-diabetes therapies (hypoglycemia, weight gain, increased risk of fractures, possible adverse cardiovascular outcomes) with those of newer treatments (lack of long term safety and efficacy data) and the benefits of newer treatments such as the low risk of hypoglycemia and the favourable impact on weight. As such, DPP-4 inhibitors are well positioned as second line therapy following metformin in patients with T2DM, particularly those who are at high risk of hypoglycemia such as the elderly and during Ramadan and also where hypoglycaemia must be avoided at all costs (e.g. living alone, occupational issues). Which DPP-4 inhibitor to use is still not clear as there are no head-to-head trials between the different agents and their safety profiles are similar.

Conclusions

Metformin is a well established first line therapy in the treatment of T2DM. Saxagliptin is a new oral anti-diabetes agent that is weight neutral and associated with low risk of hypoglycemia. Due to their complementary mechanisms of action and the lack of interference in the pharmacokinetics of either drug when combined with the other, saxagliptin is a useful second line agent to be used as an add on therapy in patients whom glycemic control is not adequately controlled by metformin alone.

Conflict of Interest

AHB has received honoraria for lectures and advisory work from MSD, Novartis, BMS-Astra Zeneca, Takeda and Servier Labs.

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