review article

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Potential for combination of dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors for the treatment of type 2 diabetes

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In individuals with advanced type 2 diabetes (T2DM), combination therapy is often unavoidable to maintain glycaemic control. Currently metformin is considered the first line of defence, but many patients experience gastrointestinal adverse events, necessitating an alternative treatment approach. Established therapeutic classes, such as sulphonylureas and thiazolidinediones, have some properties undesirable in individuals with T2DM, such as hypoglycaemia risk, weight gain and fluid retention, highlighting the need for newer agents with more favourable safety profiles that can be combined and used at all stages of T2DM. New treatment strategies have focused on both dipeptidyl peptidase (DPP)-4 inhibitors, which improve hyperglycaemia by stimulating insulin secretion in a glucose-dependent fashion and suppressing glucagon secretion, and sodium-glucose co-transporter-2 (SGLT2) inhibitors, which reduce renal glucose reabsorption and induce urinary glucose excretion, thereby lowering plasma glucose. The potential complimentary mechanism of action and good tolerance profile of these two classes of agents make them attractive treatment options for combination therapy with any of the existing glucose-lowering agents, including insulin. Together, the DPP-4 and SGLT2 inhibitors fulfill a need for treatments with mechanisms of action that can be used in combination with a low risk of adverse events, such as hypoglycaemia or weight gain.

Keywords: anti-hyperglycaemic drug, DPP-IV inhibitor, SGLT2 inhibitor, type 2 diabetes, dual inhibitor combination therapy

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Introduction

Nearly 10% of the US population has diabetes mellitus, of whom 90% have type 2 diabetes (T2DM) [1]. As the condition progresses, metabolic control often cannot be maintained with just one agent, and multiple agents are required to treat the later stages of T2DM. Based on joint guidelines issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), metformin is considered the first-line therapy unless not tolerated or contraindicated [2]. Some individuals, however, experience adverse gastrointestinal events, such as nausea, vomiting and diarrhoea, with metformin, and thus require a different treatment approach. Sulphonylureas depend on the remaining pancreatic β-cell mass and function, making them less than optimal for those with long-standing T2DM. Additionally this class of drugs is associated with hypoglycaemia and weight gain, both undesirable in the T2DM population. Thiazolidinediones, in comparison, can cause weight gain, induce fluid retention, worsen congestive heart failure and increase the incidence of bone fractures in women [3]. Thus, there is a need for newer agents with acceptable safety profiles that can be used alone or with other agents at any stage of T2DM. New treatment strategies for T2DM have largely focused on the incretin system and, despite the important role of renal pathways in glucose homeostasis, have only recently targeted the kidney [4].

Dipeptidyl peptidase (DPP)-4 inhibitors enhance postprandial insulin secretion and suppress glucagon secretion by preventing the degradation of endogenously released incretins [glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)], two intestinal peptides whose concentration increases after food intake, thus playing a vital role in glucose homeostasis [5]. DPP-4 inhibitors stimulate insulin secretion in a glucose-dependent fashion and inhibit glucagon secretion, thus minimizing hypoglycaemia and improving hyperglycaemia [6]. In addition, DPP-4 inhibitors are weight-neutral and have been shown to improve β-cell function in *in vitro* and animal studies [7,8]. These characteristics may provide benefits to those people with T2DM who have impaired β-cell function, excessive hepatic glucose production, postprandial hyperglycaemia and who are overweight or obese.

The kidney plays an important role in glucose homeostasis [9,10]. Plasma glucose is freely filtered in the kidney glomeruli and must be returned to the circulation to prevent urinary excretion. This process is accomplished with two types of carrier proteins: the active sodium-glucose co-transporters (SGLTs) and the passive glucose transporters [11–13]. The SGLT inhibitors are a family of membrane-bound transport proteins, of which SGLT type 1 (SGLT1; a low-capacity, high-affinity transporter) and SGLT type 2 (SGLT2; a

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high-capacity, low-affinity transporter) mediate glucose reabsorption from the glomerular filtrate independent of insulin and induce urinary glucose excretion (i.e. glucosuria). An indication of what to expect from pharmacological SGLT2 inhibition was derived from observations of individuals with familial renal glucosuria, a mutation of the SGLT2 gene that serves as a model for SGLT2 inhibition [8]. The impaired function of SGLT2 in affected individuals can lead to daily urinary glucose excretion of up to 200 g, but most individuals are asymptomatic and do not seem to develop significant clinical problems over time [9].These findings suggest that pharmacologic SGLT2 inhibition could be a safe option in the attempt to reduce hyperglycaemia in individuals with T2DM.

The lack of a common mechanistic pathway between SGLT2 inhibitors and other agents suggests that they can be given in combination with any of the existing therapeutic classes of glucose-lowering agents, including DPP-4 inhibitors, GLP-1 agonists and insulin. Together, the DPP-4 and SGLT2 inhibitors fulfil a need for agents with complementary mechanisms of action that can be used in combination with a low risk of adverse events, such as hypoglycaemia or weight gain. The present review provides an overview of the pharmacology, pharmacokinetics, efficacy and safety of these two classes of agents and a rationale for their use as dual-combination therapy for the treatment of T2DM.

Dipeptidyl Peptidase-4 Inhibitors

It has been more than 8 years since the first DPP-4 inhibitor, sitagliptin, was approved for the treatment of T2DM [14,15]. Currently, eight DPP-4 inhibitors are available worldwide: sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gemigliptin, anagliptin and teneligliptin. The latter three are only available in Asia [14].

In individuals with T2DM, the incretin effect is markedly impaired; whereas exogenously administered GLP-1 retains its effect and improves hyperglycaemia, the insulinoptropic effect of GIP is lost in these individuals [6]. New therapeutic advances have focused on the development of GLP-1 agonists that are resistant to DPP-4 inactivation as well as on inhibitors of DPP-4, in an effort to prevent incretins from degradation.

In addition to their glucose-dependent anti-hyperglycaemic actions that ultimately lead to reduced postprandial glucose, fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) levels, the incretins also exert beneficial pleiotropic actions on the cardiovascular system [16], including improvements in blood pressure and left ventricular function [17,18], and improved endothelium-dependent vasodilation and increased levels of endothelial progenitor cells [19,20]. Clinical trial data for DPP-4 inhibitor monotherapy have shown that these agents improve glycaemic control by reducing HbA1c [from −0.6 to −1.1% (−6.6 to 12.0 mmol/mol)] [21] and FPG concentrations (from −0.73 to −1.57 mmol/l) [21], with a similar incidence of hypoglycaemia and change in body weight as that found with placebo [22–31]. DPP-4 inhibitors are approved for treatment of hyperglycaemia as mono-, dual and triple oral therapy as well as in combination with insulin. They are usually well tolerated, and the most frequent adverse event in clinical trials was nasopharyngitis.

Sodium–Glucose Co-transporter-2 Inhibitors

Three SGLT2 inhibitors are currently approved for the treatment of T2DM in the USA and the European Union: canagliflozin, dapagliflozin and empagliflozin. These agents cause reduced reabsorption of glucose from the glomerular filtrate and increased excretion of glucose into the urine, and cause urinary glucose excretion to occur at a lower plasma glucose concentration. SGLT2 inhibition results in the loss of ~60–80 g of glucose in the urine per day [32], which helps to reduce hyperglycaemia in individuals with T2DM. In addition to improvements in glycaemic control, SGLT2 inhibitors provide other effects that are desirable in a T2DM agent, such as weight loss [33], moderate reductions in systolic blood pressure and no increase in hypoglycaemia risk [34].

Clinical trial data have shown that SGLT2 inhibitors improve glycaemic control by reducing HbA1c, postprandial glucose and FPG concentrations, and produce modest reductions in body weight and blood pressure [35–39]. When used as monotherapy, these agents have been found to lead to reductions in HbA1c [from −0.34 to −1.03% (3.7–11.3 mmol/mol)], body weight (from −2.0 to −3.4 kg), and systolic and diastolic blood pressure (from −1.7 to −6.4 mmHg and from −0.3 to −2.6 mmHg, respectively) [40]. Specific adverse reactions of SGLT2 inhibitors are related to urinary glucose excretion, in that the continual presence of glucose in the urine may increase the risk of urinary tract infections and/or genital mycotic infections.

Rationale for Combination Therapy

The progressive deterioration of β-cell function in T2DM often necessitates the use of combination therapy in order for individuals to reach their glycaemic goals; however, the use of anti-hyperglycaemic agents in combination may lead to an increase in the risk of adverse events, including weight gain and hypoglycaemia, which occur with sulphonylureas and thiazolidinediones. Individuals need treatments that can be used in combination with other agents without adverse events limiting their use. As previously mentioned, the potential complementary mechanistic pathway for SGLT2 inhibitors and DPP-4 inhibitors suggests they could be given in combination with each other without any obvious detrimental effects; however, the use of the individual agents with an insulin secretagogue or insulin may increase the risk of hypoglycaemia. Furthermore, a mechanism of action that is independent of pancreatic β-cell function makes SGLT2 inhibitors an appropriate option for those with advanced T2DM, particularly if their glycaemic control is inadequate with existing oral glucose-lowering agents.

A study assessed the effects of dapagliflozin on muscle insulin sensitivity in 18 men with T2DM [41] and found that lowering FPG using an SGLT2 inhibitor improves insulin-stimulated tissue glucose disposal. This study also showed that dapagliflozin treatment resulted in a substantial increase in endogenous glucose production, which was accompanied by an increase in fasting plasma glucagon concentrations. A study of empagliflozin that assessed the response to pharmacologically induced acute or chronic glycosuria in 66 participants with T2DM showed that glycosuria induced

by a single dose of empagliflozin lowered both FPG and postprandial glucose, despite a compensatory increase in endogenous glucose production [42]. This study also showed a glucagon increase that almost normalized after 4 weeks of empagliflozin treatment. It has been estimated that the increase in endogenous glucose production offsets approximately half of the glucose excreted as a result of SGLT2 inhibition with dapagliflozin [41]. Thus, the addition of a DPP-4 inhibitor which inhibits glucagon and stimulates insulin secretion may have the potential to block the increase in endogenous glucose production and enhance the glucose-lowering ability of SGLT2 inhibitors. Taken together, these findings suggest that the combination of an SGLT2 inhibitor with a DPP-4 inhibitor would potentially provide additional help to individuals with T2DM in reaching their glycaemic goal [41].

The combination of DPP-4 inhibitors and SGLT2 inhibitors also has the potential to exert beneficial effects on the kidney. Both classes have been reported to lower urinary albumin excretion, a risk factor for renal disease, although these findings need to be confirmed in larger studies [43–45]. A recent study in individuals with T1DM found that 8 weeks of empagliflozin treatment attenuated renal hyperfiltration, a surrogate marker of intraglomerular pressure [46]. Furthermore, the Canagliflizon and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation study (CREDENCE study; NCT02065791) with canagliflozin was recently initiated and will assess renal outcomes with SGLT2 inhibition. In addition, the CARMELINA study with linagliptin will explore the effect of DPP-4 inhibition on renal outcomes (renal death, end-stage renal disease and a sustained estimated glomerular filtration rate decrease ≥50%). The potential of combining both classes to maximize renal opportunities is intriguing and may be of interest to the readers of the present review.

Published Evidence With Combination Therapy

The drug–drug interactions of empagliflozin and linagliptin [47] or sitagliptin [48] were studied in healthy male volunteers. Both studies showed that administration of either linagliptin or sitagliptin with empagliflozin had no clinically relevant effect on the pharmacokinetics of either agent; therefore, empagliflozin can be co-administered with either linagliptin or sitagliptin without dose adjustments.

A 24-week, randomized, double-blind, placebo-controlled study assessed dapagliflozin (10 mg) as an add-on therapy to sitagliptin (100 mg, with and without metformin, ≥1500 mg/day) in 447 participants [49]. After 24 weeks, the addition of dapagliflozin significantly reduced mean HbA1c concentration compared with placebo, excluding data after rescue [placebo-corrected difference −0.5%; 95% confidence interval (CI) −0.6 to −0.3 (−6 mmol/mol; 95% CI −7 to −3); $p < 0.0001$], even in a subset of participants with HbA1c baseline levels ≥8% [≥64 mmol/mol; placebo-corrected difference −0.8%; 95% CI −1.0 to −0.6 (−9 mmol/mol; 95% CI −11 to −7); $p < 0.0001$]. Similarly, treatment with dapagliflozin also significantly decreased FPG (placebo-corrected difference −1.55 mmol/l; 95% CI −1.92 to −1.19; $p < 0.0001$) and body weight (placebo-corrected difference −1.9 kg; 95% CI −2.4 to −1.4; $p < 0.0001$). Adverse events were balanced among groups and discontinuation rates were low. These results suggest that add-on treatment with dapagliflozin in individuals inadequately controlled with sitagliptin with or without metformin can provide additional clinical benefits and is well tolerated.

Recently the combination of dapagliflozin with saxagliptin vs saxagliptin or dapagliflozin alone was assessed in a 24-week, randomized, active-controlled study in 534 participants with T2DM receiving background metformin [50]. After 24 weeks, the reductions in HbA1c from baseline [8.9, 9.0 and 8.9% (74, 75 and 74 mmol/mol), respectively], were larger in the group receiving dual combination treatment [saxagliptin 5 mg + dapagliflozin 10 mg; adjusted mean change from baseline −1.5% (−16 mmol/mol)] compared with the groups receiving either agent alone [saxagliptin −0.9% (−10 mmol/mol); difference −0.6% (−7 mmol/mol); $p < 0.0001$; dapagliflozin −1.2% (−13 mmol/mol); difference −0.3% (−3 mmol/mol); $p < 0.02$]. The adjusted proportion of participants achieving an HbA1c concentration of <7% (<53 mmol/mol) was 41% with dual combination therapy vs 18 and 22% vs saxagliptin or dapagliflozin alone, respectively. Urinary and genital infections occurred with the frequency previously reported. This study shows that, when added to background metformin therapy, the combination of a DPP-4 inhibitor and an SGLT2 inhibitor resulted in greater improvements in glucose control than each agent alone, and helped >40% of individuals achieve their glycaemic goal.

The CANagliflozin CardioVascular Assessment Study (CANVAS) is an ongoing randomized, placebo-controlled study assessing the efficacy and safety of canagliflozin 100 and 300 mg added to a range of therapies compared with placebo in patients with T2DM [51]. A *post hoc* analysis from CANVAS in individuals with T2DM and a history or high risk of cardiovascular disease assessed the effects of canagliflozin 100 and 300 mg versus placebo in subsets of participants on DPP-4 inhibitors (n = 316) or GLP-1 agonists (n = 95), with or without other antihyperglycaemic agents [52]. In that study, canagliflozin 100 and 300 mg improved HbA1c at 18 weeks compared with placebo, added to DPP-4 inhibitors [placebo-corrected change from baseline in HbA1c: canagliflozin 100 mg, −0.6% (−7 mmol/mol); 300 mg, −0.8% (−9 mmol/mol)] or GLP-1 agonists [canagliflozin 100 mg, −1.0% (−11 mmol/mol); 300 mg, −1.1% (−12 mmol/mol)]. Additionally, canagliflozin reduced body weight in both subsets (placebo-corrected change from baseline, DPP-4 inhibitors: canagliflozin 100 mg, −2.3 kg; 300 mg, −3.0 kg or GLP-1 agonists: canagliflozin 100 mg, −2.5 kg; 300 mg, −3.2 kg). Treatment was generally well tolerated. The CANVAS study continues in a blind fashion in order to collect additional safety data, including cardiovascular endpoints.

Two recent studies of the single-pill combination of empagliflozin and linagliptin assessed the efficacy and safety of empagliflozin/linagliptin in participants with T2DM [53,54]. In both studies, the primary endpoint was change from baseline in HbA1c. The key secondary endpoints included changes from baseline in FPG and body weight, as well as the percentage of participants with HbA1c ≥7.0% (53 mmol/mol) at baseline who achieved an HbA1c target of <7% (<53 mmol/mol), all assessed at week 24. One study randomized drug-naïve

individuals with T2DM to receive empagliflozin/linagliptin (25 mg/5 mg, n = 137 or 10 mg/5 mg, n = 136), empagliflozin alone (25 mg, n = 135 or 10 mg, n = 134) or linagliptin alone (5 mg, n = 135) [53]. Both single-pill combinations significantly reduced HbA1c from baseline [from 7.99 to 8.05% (64 mmol/mol)] compared with linagliptin alone [25 mg/5 mg, difference −0.4% (−4 mmol/mol); $p < 0.001$; 10 mg/5 mg, difference −0.6% (−7 mmol/mol); $p < 0.001$]. HbA1c reductions were greater with empagliflozin/linagliptin 10 mg/5 mg than with empagliflozin 10 mg [difference −0.41% (−4.5 mmol/mol); $p < 0.001$], but were not significantly different between empagliflozin/linagliptin 25 mg/5 mg and empagliflozin 25 mg [difference −0.14% (−1.5 mmol/mol); p = non-significant]. The single-pill combinations also caused greater reductions in FPG and body weight than linagliptin alone. In addition, the proportion of individuals who achieved their goal HbA1c concentration [<7% (<53 mmol/mol)] at 24 weeks was significantly greater with the single-pill combination than with the individual components: 55.4 and 62.3%, respectively, for the empagliflozin/linagliptin 25 mg/5 mg and 10 mg/5 mg groups compared with 41.5, 38.8 and 32.3%, respectively, for the empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg groups. Confirmed hypoglycaemic adverse events [glucose ≤3.8 mmol/l (70 mg/dl) and/or requiring assistance] were reported in two subjects on empagliflozin 25 mg and one each on empagliflozin 10 mg and linagliptin 5 mg; none required assistance.

The second study assessed the single-pill combination of empagliflozin and linagliptin as an add-on to stable metformin in participants with T2DM [54]. In 674 participants, the single-pill combinations significantly reduced HbA1c compared with the respective monotherapies: empagliflozin/linagliptin 25 mg/5 mg vs empagliflozin 25 mg [difference −0.58% (−6.3 mmol/mol); $p < 0.001$] and vs linagliptin 5 mg [difference −0.50% (−5.5 mmol/mol); $p < 0.001$]; empagliflozin/linagliptin 10 mg/5 mg vs empagliflozin 10 mg [difference −0.42% (−4.6 mmol/mol); $p < 0.001$] and vs linagliptin 5 mg [difference −0.39% (−4.3 mmol/mol); $p < 0.001$]. Combination treatment also lowered FPG compared with the individual agents and body weight vs linagliptin. In addition, the proportion of participants who were at goal [HbA1c <7% (<53 mmol/mol)] at 24 weeks was significantly greater with the single-pill combination than with the individual components: 61.8 and 57.8%, respectively, for the 25 mg/5 mg and the 10 mg/5 mg groups compared with 32.6, 28.0 and 36.1%, respectively, for the empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg groups. Confirmed hypoglycaemic adverse events [glucose ≤ 3.8 mmol/l (70 mg/dl) and/or requiring assistance] were reported in two subjects each on empagliflozin/linagliptin 25 mg/5 mg, empagliflozin/linagliptin 10 mg/5 mg and empagliflozin 10 mg and linagliptin 5 mg, and four subjects on empagliflozin 25 mg; none required assistance.

Glycaemic control with empagliflozin/linagliptin was maintained at week 52 with statistically significant improvements from baseline in HbA1c, and a higher proportion of individuals achieving HbA1c <7% [53 mmol/mol], in both single-pill combination groups vs the linagliptin 5 mg group, and the empagliflozin 10 mg/linagliptin 5 mg group vs empagliflozin 10 mg group [53], and for the empagliflozin 25 mg/linagliptin 5 mg combination vs the empagliflozin 25 mg group in the metformin add-on study [54]. In addition, all therapies were well tolerated.

New Clinical Studies With Combination Therapy

A number of clinical trials assessing the combination of DPP-4 inhibitors with SGLT2 inhibitors in T2DM are underway. Two studies are investigating the efficacy and safety of adding on empagliflozin to linagliptin vs linagliptin alone (NCT01734785) and adding on linagliptin to empagliflozin vs empagliflozin alone in participants with T2DM (NCT01778049), both studies are scheduled to be completed in 2015. Several other ongoing studies are assessing the combination of dapagliflozin and saxagliptin; NCT01662999 is looking at the drug interaction of both agents in healthy individuals. Other phase III studies that are currently recruiting include assessments on the efficacy and safety of saxagliptin (NCT01619059) or dapagliflozin (NCT01646320) in triple therapy in participants with T2DM who have inadequate glycaemic control with dual therapy including metformin.

Clinical Application

Combination therapy with DPP-4 and SGLT2 inhibitors may prove to be a useful approach in a broad range of participants, such as those insufficiently controlled with metformin as dual or triple therapy or those with a contraindication or intolerance to metformin. Combination therapy using agents with complementary mechanisms of action is recommended in the 2013 American Association of Clinical Endocrinologists' Comprehensive Diabetes Management Algorithm [55] as well as in the 2015 Position Statement of the ADA/EASD [2]. In addition, initial combination therapy is recommended for those with an HbA1c ≥7.5% [55] or ≥9.0% [2], either with metformin or other background treatment for those unable to use metformin.

Other populations who could benefit from this combined oral treatment approach include those desiring to lose weight or to offset any potential weight gain with other oral anti-hyperglycaemic agents or insulin, those with advanced T2DM inadequately controlled on their antihyperglycaemic regimen, including participants who would otherwise need to progress to insulin therapy but are unwilling or unable to commence injections, and older individuals at high risk of hypoglycaemia. There are several barriers to achieving target glycaemic control in diabetic individuals. Use of multiple oral agents can increase the efficacy of treatment but can also cause more adverse events and increase the pill burden; therefore, choosing oral agents which can be combined safely is important. Among the oral agents, sulphonylureas can cause weight gain, hypoglycaemia and are associated with progressive β-cell failure in the long run and thiazolidinediones can cause fluid retention and weight gain. DPP-4 inhibitors and SGLT2 inhibitors are well tolerated, weight-neutral and have a low propensity for hypoglycaemia; hence, their combination can help improve glycaemic control while avoiding some of the trade-offs of the traditional oral glucose-lowering treatments.

A single-pill combination of a DPP-4 inhibitor and a SGLT2 inhibitor, when available, would offer several advantages over the free combination of individual pills, including a reduced pill burden, which could possibly translate into improved compliance.

In summary, combining DPP-4 inhibitors with SGLT2 inhibitors has the potential to exert benefits beyond lowering glucose, such as beneficial effects on cardiovascular and renal risk factors, including albuminuria, and lowering body weight and systolic blood pressure.

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Conflict of Interest

Boehringer Ingelheim Pharmaceuticals, Inc. was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. The author has served on the speaker's bureau for Boehringer Ingelheim Pharmaceuticals, Inc. and Bristol-Myers Squibb.

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