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REVIEW

DPP4 Inhibitors: from Sitagliptin Monotherapy to the New Alogliptin-Pioglitazone Combination Therapy

Georgia Argyrakopoulou · John Doupis

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ABSTRACT

Diabetes mellitus (DM) is currently considered to be an epidemic disease. A safe and effective treatment has long been sought by scientists. Incretin mimetics and dipeptidyl peptidase-4 (DPP4) inhibitors represent a new class of agents that have recently been included as antidiabetic drugs. Although only a limited number of studies exist regarding the treatment of DM based on the incretin effect, DPP4 inhibitors have so far proved to be safe and effective, both when administered alone or in combination with other antidiabetic medication. This review focuses on incretin-effect physiology, as well as the DPP4 inhibitors, from sitagliptin to the new alogliptin-pioglitazone combination agent, given as monotherapy and in combination with other antidiabetic agents.

Georgia Argyrakopoulou
Laikon Hospital, Kapodistriakon University Medical School, Athens, Greece

John Doupis (✉)
Joslin Diabetes Center, Harvard Medical School, 1 Joslin Place, Boston, Massachusetts 02215, USA.
Email: John.Doupis@joslin.harvard.edu

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INTRODUCTION

Diabetes mellitus (DM) is considered to be one of the most rapidly increasing diseases in terms of prevalence, and its treatment is evolving.[1] Scientists are awaiting the clinical results of recent scientific progress that has been made in the diabetes field, which includes the discovery of the role of gut peptides.[2] However, limited studies exist and scientists are continuously making efforts to shed light on this new strategy for the treatment of DM.

INCRETIN HORMONES

Glucose induces a greater increase in plasma insulin levels when administered orally than when the same amount of glucose is administered intravenously; this is defined as the incretin effect.[2] The two known incretin hormones are glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). GLP-1 is secreted from

the L-cells, which are principally localized at the ileum and colon, while GIP is secreted from the K-cells, which are mainly placed at the duodenum and proximal jejunum of the small intestine.[2,3] However, cells secreting both incretins are found throughout the small intestine. GIP receptors are expressed in the pancreatic cells, intestine, fat tissue, heart, pituitary gland, adrenal cortex, and in the brain.[2,4,5] GLP-1 receptors are expressed in the gastrointestinal tract, α-cells and β-cells of the pancreas, the lungs, kidneys, heart, and in some brain regions.[4-6]

The primary stimulus of incretin secretion is food consumption, in particular fat and carbohydrate.[7] The action of incretins is insulin dependent and ends when glucose levels are <55 mg/dL.[8] Oral ingestion of nutrients promotes GLP-1 secretion in a biphasic pattern, including an early (10-15 minutes) phase and a later (30-60 minutes) phase.[2] Considering the distal location of the majority of L-cells, and the within-minutes secretion, the early phase of GLP-1 secretion is probably mediated indirectly through neuronal and endocrine mechanisms, including the autonomic nervous system (probably via the vagus nerve and various neurotransmitters).[9] However, as described previously, L-cells are located throughout the intestine. Therefore, the early phase of the GLP-1 secretion could also be nurtured via a direct effect.[2] Conversely, the late-onset phase is mediated by the direct contact of nutrients with the L-cells.[3] Other GLP-1 in-vitro or in-vivo stimuli include leptin (leptin receptors are expressed in L-cells), and numerous intracellular signals (protein kinase A [PKA], protein kinase C [PKC], calcium, and mitogen-activated protein kinase [MAPK]).[2] By contrast, insulin and somatostatin have been reported to be GLP secretion inhibitors.[2] Biologically active forms of GLP include GLP-1(7-37) and GLP-1(7-36)NH2. The latter constitutes the most frequent form of GLP-1 found in humans.[10] However, GLP-1 has a half-life of less than 2 minutes.

GLP-1 is mainly excreted through the kidneys[11] and it has been shown that renal failure patients have increased GLP-1 metabolite concentration, while bioactive GLP-1 levels are similar to those of healthy individuals.[12] GIP and GLP-1 levels are low in the fasting state and increase twofold to threefold after meal ingestion, depending on the size and type of meal.[13] Obese individuals and patients with type 2 diabetes (DMT2) have decreased postprandial levels of GLP-1, probably because of reduced GLP-1 secretion.[14,15]

GLP-1 exhibits various actions including: promotion of insulin biosynthesis and glucose-induced insulin secretion; improvement of glucose response of resistant pancreatic β-cells; inhibition of glucagon secretion (a glucose-dependent effect that is probably induced via insulin and somatostatin secretion); and stimulation of somatostatin secretion (a non-glucose-level dependent effect).[6] GLP-1 also increases β-cell mass via stimulation of β-cell proliferation, and neogenesis and inhibition of β-cell apoptosis.[6] GLP-1 slows gastric emptying and intestinal glucose absorption.[6] Peripheral administration of GLP-1 receptor agonists promotes satiety, reduces energy intake, and leads to weight loss in healthy individuals, patients with DM, as well as in obese individuals.[16]

GIP increases glucose-dependent insulin secretion and upregulates β-cell proliferation.[6] GIP also promotes insulin-stimulated incorporation of fatty acids into triglycerides and stimulates lipoprotein lipase activity, enhancing fatty acid formation.[6] However, GIP does not alter pancreatic α-cell secretion of glucagon or gastric emptying.[6] In diabetic

patients, GIP levels are normal or increased, while meal-stimulated plasma levels of GLP-1 are moderately but significantly reduced in patients with impaired glucose tolerance (IGT) and in diabetics.[14]

DIPEPTIDYL PEPTIDASE-4

Dipeptidyl peptidase-4 (DPP4) is a serine protease found in several tissues, including the kidneys, intestine, hepatocytes, vascular endothelium, membranes, and lymphocytes.[17,18] DPP4 also exists in a soluble circulating form within plasma.[17] The action of DPP4 is performed by cleavage of the two N-terminal amino acids, providing that the second amino acid is either proline or alanine, which is the case for GLP-1.[19] GIP and GLP-1 are rapidly inactivated by DPP4, which cleaves these two terminal amino acids from the biologically active forms, inactivating the incretin hormones.[20] GLP-1 is metabolized into GLP-1(9-37) or GLP-1 (9-36)NH2.

The enzyme DPP4 is widely expressed in numerous tissues, including the vascular endothelium of the intestine, where sites of GLP secretion are found. Therefore, the majority of GIP and GLP-1 have been inactivated before entering circulation. As mentioned above, DPP4 has the ability to inactivate incretin hormones but has also been found to act on the metabolism and activation of other peptides such as neuropeptide Y, peptide YY, gastric releasing polypeptide, and insulin-like growth factor-I.[6]

DPP4 Inhibitors

DPP4 inhibitors are reversible competitive inhibitors of the DPP4 molecules, and have recently been included in the therapeutic group of agents used in DM treatment.[21] These include sitagliptin, vildagliptin, alogliptin, and various others such as saxagliptin and linagliptin, which are still under development.[22] DPP4 inhibition is a dose-dependent and long-lasting process in healthy individuals as well as patients with DMT2.[22] The effect of DPP4 inhibitors may be mediated via enhancement of GLP-1 secretion.[22] Sitagliptin is used as a DMT2 drug and shows high selectivity for DPP4.[22] Sitagliptin is mainly excreted by the kidneys while 25% of the drug is metabolized by the hepatic CYP 3A4 and CYP 2C8 cytochromes.[22] Vildagliptin is another potent DPP4 inhibitor that is metabolized by the liver and excreted mainly through the kidneys.[22]

Sitagliptin and vildagliptin are rapidly absorbed and orally bioavailable. In patients with renal impairment, a dose adjustment seems to be necessary.[23,24] Vildagliptin is not recommended for patients with liver insufficiency, while both vildagliptin and sitagliptin are not recommended in patients with severe kidney impairment.[21] Inhibition of DPP4 activity by both sitagliptin and vildagliptin takes place 15-30 minutes after oral ingestion and more than 80% of this inhibition lasts for >16 hours, through an initial phase of rapid binding and a slow phase of very tight binding kinetics.[25] Furthermore, age, gender, ethnicity, and body mass index do not seem to have an influence in the pharmacokinetics of the aforesaid molecules.[21] Given that DPP4 inhibitors act on incretin secretion, they should be initiated at early stages of DMT2 therapy.[26]

Sitagliptin

Sitagliptin is available for use in DM therapy as an oral agent, as well as in combina-

tion with metformin. Sitagliptin monotherapy in DMT2 patients showed significant reductions in glycated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in an 18-week and a 24-week study when compared with placebo.[27,28] Homeostasis Model Assessment (HOMA) of β-cell function and proinsulin-to-insulin ratio improved, while hypoglycemia and body weight were not increased.[27,28] Gastrointestinal adverse events were not significantly higher with sitagliptin.[27-29] However, other adverse events, including upper respiratory symptoms, urinary tract infection, and myalgias were slightly increased in the sitagliptin groups compared with placebo.[27,28]

Similar conclusions were extracted by a 24-week study of sitagliptin added to ongoing metformin therapy in patients with DMT2 who were not sufficiently controlled with metformin monotherapy.[29] Sitagliptin significantly reduced $HbA_{1c,}$ fasting plasma glucose, 2-hour postmeal glucose, and insulin sensitivity indices compared with placebo.[29] The addition of sitagliptin versus glipizide to ongoing therapy with metformin, provided similar HbA_{1c}-lowering efficacy over a 52-week study period.[30] However, use of sitagliptin produced a lower risk of hypoglycemia compared with glipizide, and resulted in weight loss, whereas use of glipizide resulted in weight gain.[30]

Comparable results in HbA_{1c}, fasting plasma glucose, 2-hour postmeal glucose, and insulin sensitivity indices were shown in a 24-week study in patients with DMT2 and inadequate glycemic control with ongoing pioglitazone treatment, after the addition of sitagliptin.[31] One could therefore conclude that sitagliptin is a relatively safe antidiabetic agent, producing well-tolerated antidiabetic effects, either alone or in combination with other antidiabetic agents such as metformin or pioglitazone.

Vildagliptin

Studies concerning vildagliptin have shown similar results. Ristic et al. showed that the use of vildagliptin in DMT2 patients significantly decreased HbA_{1c} levels, improving the HOMA index, mean 4-hour postprandial glucose, and levels of insulin, compared with the placebo group.[32] In a 24-week study in DMT2 patients, in which vildagliptin was compared with placebo in drug-naïve patients, HbA_{1c} and fasting plasma glucose were significantly reduced in the vildagliptin group. Body weight was not altered in the vildagliptin group, whereas it was reduced in the placebo group. Adverse events were apparent with similar frequency in both groups.[33] A 12-week study comparing vildagliptin with placebo in 179 subjects with IGT showed that vildagliptin increased GLP-1 and GIP, decreased glucagon, and did not affect postprandial insulin levels compared with placebo.[34] β-Cell function was significantly increased in the vildagliptin group and adverse events were similar in the two treatment groups.[34]

A study comparing metformin and vildagliptin monotherapies showed a decrease in HbA_{1c} levels and a sustained efficacy throughout a 1-year treatment with both agents. However, statistical noninferiority of vildagliptin to metformin (at a dose of 50 mg twice daily and 1000 mg twice daily, respectively) could not be established.[35] Furthermore, body weight was only decreased in metformin-treated patients.[35] In a 12-week study with a 40-week extension period, placebo or vildagliptin were added to metformin treatment and were assessed performing meal tests, consuming a standardized 465-kcal breakfast meal, at 0, 12, 24, and 52 weeks. The vildagliptin/metformin group exhibited a decrease in HbA_{1c} and fasting

plasma glucose, while the placebo/metformin group experienced an increase.[36] Insulin secretion, β-cell function, and postmeal insulin sensitivity were also improved in the vildagliptin/metformin group.[36]

In a comparison study of vildagliptin versus pioglitazone as add-on therapy in patients with DMT2 who were inadequately controlled with metformin monotherapy, a decrease in HbA_{1c} was produced by both drugs. In addition, pioglitazone decreased fasting plasma glucose and increased body weight more than vildagliptin.[37] In a 24-week study comparing pioglitazone, vildagliptin, and their combination in drug-naïve patients with DMT2, it was reported that the combination was significantly more efficacious in decreasing HbA_{1c} and fasting plasma glucose than pioglitazone alone.[38] Interestingly, the incidence of peripheral edema was highest in patients receiving pioglitazone monotherapy and lowest in those receiving low-dose combination therapy.[38] The combination of vildagliptin with pioglitazone in DMT2 patients who were inadequately treated with pioglitazone has also been evaluated.[39] HbA_{1c}, fasting plasma glucose, and postprandial glucose were reduced in patients receiving the combination therapy.[39] Furthermore, the insulin secretory rate/glucose ratio was increased by more than threefold.[39] In DMT2 patients who were inadequately controlled by insulin, the addition of vildagliptin to insulin therapy decreased HbA_{1c} levels compared with the group receiving placebo plus insulin.[40] Interestingly, hypoglycemia was less frequent or severe in those receiving vildagliptin and insulin.[40] Vildagliptin as an add-on to metformin, showed a decrease in HbA_{1c} and fasting plasma glucose compared with placebo. Moreover, the drug seemed to be very well tolerated.[41]

Saxagliptin

Saxagliptin has also been evaluated in a 6-week (100 mg once daily) and a 12-week (2.5, 5, 10, 20, or 40 mg once daily), double-blind, placebo-controlled study in drug-naïve DMT2 patients with inadequate glycemic control. Saxagliptin significantly reduced HbA_{1c} levels and fasting plasma glucose compared with placebo.[42] Moreover, postprandial glucose levels (1 hour after a liquid meal) were also found to be decreased compared with placebo.[42] Saxagliptin did not alter body weight. Adverse events were similar in both groups, with a very low incidence of confirmed hypoglycemia in the saxagliptin treatment group.[42]

Alogliptin

Alogliptin is a potent, selective inhibitor of DPP4. It has been shown that a single oral dose produces a sustained decrease in plasma DPP4 activity and blood glucose.[43] Limited studies have been conducted so far, studying alogliptin alone or in combination therapies in animals and humans. Alogliptin potently inhibits human DPP4 in vitro and exhibits >10,000-fold selectivity for DPP4 over other closely-related serine proteases.[43] Absolute oral bioavailability of alogliptin in rats, dogs, and monkeys was found to be 45%, 86%, and 72%-88%, respectively.[43] After a single oral dose of alogliptin, plasma DPP4 was inhibited within 15 minutes. Maximum inhibition was >90% in rats, dogs, and monkeys and was maintained for 12 hours in rats and dogs, and 24 hours in monkeys.[43] In Zucker fa/fa rats, a single dose of alogliptin inhibited DPP4 levels increased plasma GLP-1 concentration, increased first-phase insulin secretion, and decreased glucose levels after oral glucose chal-

lenge.[43] However, alogliptin at doses of 30 and 100 mg/kg did not show any effect on fasting glucose levels in normoglycemic rats.[43] In a randomized, double-blind, placebo-controlled study in healthy, nonobese male subjects (aged 18-55 years) treated with alogliptin on various dosages (25, 50, 100, 200, 400, or 800 mg, or placebo), it was reported that the drug was very well tolerated. Increase of C_{max} (maximum concentration observed) and $AUC_{0\text{-infinity}}$ (area under the curve, 0 to infinity) were found to be dose-dependent over 25-100 mg.[44] Mean peak DPP4 inhibition was found to be 93%-99% and mean inhibition at 24 hours after dosing was 74%-97%.[44] Active GLP-1 exposure was not dose-dependent and was found to be two- to fourfold greater for all aforementioned alogliptin doses versus placebo administration.[44] Adverse effects included asymptomatic hypoglycemia, syncope (in the 200 mg dose), constipation, and viral infection.[44]

In another randomized, double-blind, placebo-controlled study alogliptin was administered in DMT2 patients (aged 18-75 years) in oral doses of 25, 100, and 400 mg, or placebo for 14 days.[45] At the concluding day of the study (day 14), mean peak DPP4 inhibition was found between 94% and 99% while mean inhibition at 24 hours after dosing was 82% -97% in all alogliptin doses.[45] Mean 4-hour postprandial plasma glucose was reduced after breakfast, lunch, and dinner with all doses of alogliptin, compared with placebo. Significant decreases in mean HbA_{1c} were also apparent in patients receiving alogliptin compared with placebo.[45] However, mean 4-hour postprandial insulin and mean fasting C-peptide were not statistically significantly altered. The most common adverse effects were headache, dizziness, and constipation.[45]

In an interesting combination study testing alogliptin with pioglitazone in ob/ob mice, glycemic control, lipid profiles, and pancreatic insulin content were improved via inhibition of incretin inactivation in alogliptin, and by improving insulin resistance in pioglitazone.[46] Active GLP-1 levels were increased, and glucagon showed a decrease after 4-5 weeks of treatment with alogliptin.[46] By contrast, pioglitazone increased plasma adiponectin levels.[46] Combination treatment increased insulin levels by 3.2-fold and decreased HbA_{1c} by 2.3%, and nonfasting and fasting plasma glucose by 37% and 62%, respectively.[46] Their effect on fat was also exhibited through the decrease of plasma triglycerides by 67% and non-esterified fatty acids by 25%. Pancreatic insulin content was increased by 2.2-fold, which was not followed by significant changes in body weight. Another study tested the effect of alogliptin (12.5 mg and 25 mg of alogliptin vs. placebo for 26 weeks) in drug-naïve patients with poorly controlled DMT2.[47] Mean change in HbA_{1c} and fasting plasma glucose was significantly reduced in patients using alogliptin vs. placebo.[47] The overall incidences of adverse events and hypoglycemia did not differ between the groups.[47]

CONCLUSIONS

As many clinical studies have shown, as a new therapeutic approach for DMT2 DPP4 inhibitors have been proved to be very beneficial in achieving glycemic control. Furthermore, they provide good tolerability either as monotherapy or as a combined therapy with other antidiabetic agents. Apart from the glucose-lowering effect, one of their main advantages is that their action is glucose-dependent, thus the danger of hypoglycemia is low. DPP4 inhibitors can be used

early after the diagnosis of DMT2, either as monotherapy in conjunction with diet and exercise, or in combination with metformin or thiazolidinedione when adequate glycemic control is not achieved with a single agent. Their use could also be expanded as a combination therapy with insulin, with excellent results in glycemic control.

As limited studies exist so far regarding this promising family of antidiabetic agents, especially the new combined drugs with metformin or thiazolidinedione, research should be focused in this direction in order to further enrich our knowledge and provide more information relating to their clinical efficacy for the treatment of DMT2.

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