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Editorial

Dipeptidyl Peptidase 4 Inhibitors for the Treatment of Type 2 Diabetes Mellitus: Focus on Efficacy, Disposition and Safety

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Diabetes mellitus is a major health problem around the world, with continued expansion of diabetes mellitus associated morbidity, mortality, reduced quality of life and increased healthcare costs. Based on the data from the 2011 National Diabetes Fact Sheet in the US (http://www.cdc.gov/diabetes/pubs/factsheet11.htm), 25.8 million children and adults (i.e. 8.3% of the population) have diabetes, and 1.9 million new cases of diabetes are diagnosed in people aged 20 years and older in 2010. A total of 25.6 million or 11.3% of US people aged 20 years and older have diabetes. Excluding accidents, diabetes is the fifth cause of death for women and the fourth for men in the US. In adults, type 2 diabetes (previously called non–insulin-dependent diabetes mellitus or adult-onset diabetes; T2DM) accounts for about 90–95% of all diagnosed cases of diabetes. T2DM is a chronic metabolic disorder characterized by progressive hyperglycemia secondary to declining β-cell function, and usually accompanied by a reduced sensitivity to insulin in peripheral tissues, such as liver and muscle [1].

Dipeptidyl Peptidase 4 (DPP-4, also known as adenosine deaminase complexing protein 2 or lymphocyte cell surface protein CD26) is a serine protease that is widely distributed throughout the body, expressed as an enzyme on endothelial cells, on the surface of T lymphocytes, and in a circulating form [2,3]. As a membrane-spanning, cell-surface aminopeptidase, it is ubiquitously expressed in many tissues, such as gut, lymphocyte, liver, kidney, and lung.DPP-4 cleaves the two *N*-terminal amino acids from peptides with a proline or alanine in the Penultimate (P_1) position. Although there are many other potential substrates including growth factors, chemokines, neuropeptides, and vasoactive peptides for this enzyme, it appears to be especially critical for the inactivation of Glucagon-like Peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (also known as Gastric Inhibitory Polypeptide, GIP) [2,3].GLP-1 and GIP are intestinal incretin hormones released in response to food ingestion [4]. Both GLP-1 and GIP enhance meal-related insulin secretion and promote glucose tolerance [3,4]. Besides insulin secretion enhancement via cAMP-dependent signaling pathways, GLP-1 also suppress glucagon secretion from α-cells in the islets of Langerhans in the pancreas in a glucose-dependent manner, and glucagon secretion is inhibited under hyperglycemic conditions and even increased under hypoglycemia. Moreover, GLP-1 slows gastric emptying and gastrointestinal motility, gastrointestinal motility, suppressing the rise of blood glucose level [4]. Therefore, DPP-4 inhibitors have been developed and used to prevent degradation of endogenously released GLP-1 and GIP, and consequently enhancing plasma level of active incretins in circulation, prolonging the actions of the incretin, finally leading to increased insulin level [5].

DPP-4 inhibitors have been shown to improve glycemic control without increasing hypoglycemic risk or causing weight gain in patients T2DM [6-8]. So far, eight DPP-4 inhibitors have been approved for clinical use, including alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin. All these gliptins except anagliptin, gemigliptin and teneligliptin are available in the US. Sitagliptin was the first gliptin approved by the Food and Drug Administration (FDA) of the United States in October 2006 and is now available worldwide. Vildagliptin and saxagliptin were approved by the FDA in February 2008 and July 2009, respectively. Alogliptin was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in April 2010 and by the FDA in January 2013. Anagliptinis available only in Japan since it was approved by the PMDA in September 2012 and linagliptin was authorized by the FDA in May 2011. Gemigliptin was co-developed by LG Life Science and Double-Crane Pharmaceutical Co. and gained approval from Korea Food & Drug Administration in June 2012. DPP-4 inhibitors may be used as a monotherapy or in double or triple combination with other oral antidiabetic agents such as metformin, thiazolidinediones, or sulfonylureas.

DPP-4 inhibitors are all small molecules used orally with similar overall clinical efficacy and safety profiles in patients with T2DM [8]. DPP-4 inhibitors may be classified into peptidomimetic (i.e, sitagliptin, teneligliptin, vildagliptin, saxagliptin, and anagliptin) and non-peptidomimetic (i.e, alogliptin and linagliptin) subtypes. Due to the substrate site specify, many DPP-4 inhibitors have substituted pyrrolidines or thiazolidines as a proline mimetic in the P_1 part. DPP-4 inhibitors developed initially possess an electrophilic trap such as a nitrile group to form a covalent bond with Ser630 of the

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catalytic triad in the active site, but these DPP-4 inhibitors possessing the electrophilic trap are unstable and have a low selectivity against DPP-8 and DPP-9. Inhibition of DPP-8 and DPP-9 are associated with multiorgan toxicities in rats and dogs and inhibition of T cell activation and proliferation [9], and a high DPP-4 selectivity is critical for DPP-4 inhibitor development and clinical application.

Although DPP-4 inhibitors have the same mode of action, they differ in pharmacokinetic and pharmacodynamic properties that may be clinically relevant [7,8,10]. All DPP-4 inhibitors except vildagliptin (twice daily) are generally taken once a day. DPP-4 inhibitors reduce plasma DPP-4 activity by 70–93% in a sustained manner for 24 hr with an increase of GLP-1 levels (1.5- to 4-fold) [9]. Following oral administration in humans, most DPP-4 inhibitors are well absorbed with oral bioavailability ranging from 29.5% for linagliptin to 100% for alogliptin and are not significantly affected by food ingestion [7]. All gliptins are bound to plasma proteins to certain extents, with teneligliptin having the highest binding to plasma proteins (77.6-82.2%) followed by linagliptin (70%). The apparent Volume of distribution (V_d) of gliptins ranges from 70.5 L for vildagliptin to 368-918 L for linagliptin and 417 L for alogliptin [2]. Linagliptin has the longest half-life (120–184 hr), followed by teneligliptin (24.2 hrs), alogliptin (21.1 hr), and gemigliptin (16.6–20.1 hr), while anagliptin, saxagliptin and vildagliptin have shorter half-lives of 2.2-4.4 hr [9].

Saxagliptin, teneligliptin and vildagliptin are extensively metabolized in the liver, while other gliptins undergo minimal to moderate biotransformation in the body [1]. Saxagliptin is mainly metabolized by cytochrome P450 (CYP3A4/5) to 5-hydroxy saxagliptin, which is 50% as potent as the parent drug [11]. Alogliptin is also metabolized by CYP3A4/5 and 2D6 to an active metabolite, M-I, which is about 3% as potent as the parent drug. Sitagliptin is a substrate of CYP3A4/5 and 2C8, and teneligliptin is metabolized by CYP2D6 and flavin-containing monooxygenases 1 & 3 (FMO1 & FMO3 to multiple inactive metabolites [12].

All DPP-4 inhibitors except linagliptin (5%) and teneligliptin (35.8%) predominantly (63.3-87%) undergo renal excretion, with 50-95% of the total dose eliminated as unchanged parent drug in the urine and feces [7]. Notably, linagliptin is excreted mostly (~90%) unchanged in feces via biliary excretion, and appears to be safe in diabetic patients suffering from renal insufficiency. An appropriate dose reduction of the gliptins with predominantly renal excretion (sitagliptin, saxagliptin and alogliptin, but not vildagliptin) is needed in T2DM patients with renal impairment [5]. In patients with mild to severe liver impairment, no dose adjustment appears necessary for linagliptin despite its remarkable hepatic excretion.

Clinically approved DDP-4 inhibitors are generally well tolerated in T2DM patients [5,12]. As a drug class, the DPP-4 inhibitors have become accepted in clinical practice due to their excellent tolerability profile, with a low risk of hypoglycemia, a neutral effect on body weight, and once-daily dosing. The insulin-release effects of the incretins are glucose-dependent and have no insulinotropic activity at lower glucose concentration (<4 mM), therefore reducing the chance of hypoglycemia, which is one of the major concerns of other antidiabetic drug classes [12].

Hypoglycemic events are mainly observed when DPP-4 inhibitors are associated with sulfonylureas (in 20% of the patients treated in combination) DDP-4 inhibitors can cause mild to moderate adverse effects, including headache, nausea, vomiting, and urinary tract infection [12].

Other adverse effects of DDP-4 inhibitors, including hypersensitivity reactions (e.g. angioedema and Stevens–Johnson syndrome) and acute pancreatitis have been reported post-marketing [6,12]. However, it is unclear if DDP-4 inhibitors increase the risk of cancer in T2DM patients. These effects may be associated with the inhibitory activity of DDP-4 on the inflammatory actions of the chemokine CCL11/eotaxin [12]. Careful long-term surveillance on the safety profile of DPP-4 inhibitors is mandatory.

Diabetic patients are at increased risk of cardiovascular diseases. Rosiglitazone was been withdrawn from the market in the European Union in 2010, because of a possible increased risk of ischemic heart disease associated with its use. Several preclinical and clinical studies have suggested a possible beneficial effect on cardiovascular risk associated with DPP-4 inhibitors, which also seem to possess a direct effect on the heart, independent of the incretin system [13]. They may exert some favorable effects on risk factors, resulting in a reduction of blood pressure, an improvement of postprandial lipid levels, and a reduction of high-sensitivity C-reactive protein. In addition, the endothelial dysfunction is also improved by gliptins.

The DPP-4 inhibitors represent a highly promising, novel class of oral agents for the treatment of T2DM. Their novelty lies in their dual action on α- and β-cell function, leading to an improved profile of glucagon and insulin secretion patterns after meal [8,9,14]. These drugs are weight-neutral, do not cause hypoglycemia, and are not associated with severe gastrointestinal adverse events [1]. The National Institute for Health and Clinical Excellence (NICE) clinical guideline for T2DM issued in 2009 in the United Kingdom http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12165 suggests adding a DPP-4 inhibitor instead of a sulfonylurea as a second-line treatment to first line metformin if there is a considerable risk for hypoglycemia or if a sulfonylurea is contraindicated or not tolerated. Data from long-term clinical studies are not yet available to determine the sustainability of glycemic control and protection of β-cell mass. The interference of the DPP-4 inhibitors with immune function is poorly understood and warrants further careful evaluation. Another potential disadvantage is a higher cost per day of clinical use as compared to insulin, metformin, or pioglitazone, which is an economic drawback for the DPP-4 inhibitors.

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