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Linagliptin: Effectiveness for glycemic control, safety, and cardiovascular risk factors in patients with type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus is a chronic, progressive disease that accelerates the atherosclerosis process and promotes the development of different complications (diabetic nephropathy, diabetic neuropathy, etc.). In these diseases, advanced atherosclerosis is not uncommon and increases the cardiovascular risks such as coronary disease and stroke.

In a similar manner, other concurrent chronic diseases also increase cardiovascular risk such as hypercholesterolemia, albuminuria, and hypertension that also affect a high percentage of patients with type 2 diabetes mellitus. Furthermore, some side effects inherent to type 2 diabetes mellitus treatment (particularly isolated or recurrent hypoglycemia) also increase cardiovascular risk in diabetic patients.

The main objectives of this article are to: (i) assess the effectiveness on glycemic control and safety of linagliptin in accordance with its low risk of body weight gain and hypoglycemia; and (ii) review the effectiveness of linagliptin for controlling cardiovascular risk factors such as hypertension,

RESUMEN

La diabetes *mellitus* tipo 2 (DM2) es una enfermedad crónica y progresiva; que acelera el proceso de aterosclerosis y promueve el desarrollo de diferentes complicaciones (nefropatía, neuropatía y retinopatía diabéticas, etc.), en las que no es inusual la aterosclerosis avanzada, la cual aumenta el riesgo cardiovascular, es decir, la aparición de condiciones tales como la enfermedad coronaria y la enfermedad cerebrovascular.

Asimismo, altos porcentajes de pacientes con DM2 se ven afectados por otras enfermedades crónicas concomitantes que también incrementan dicho riesgo, entre ellas hipercolesterolemia, albuminuria e hipertensión arterial.

Pero no solo las complicaciones de la DM2 y sus comorbilidades frecuentes incrementan sustancialmente el riesgo cardiovascular, puesto que algunos de los efectos secundarios inherentes al tratamiento estricto de la DM2 (principalmente la hipoglucemia aislada o recurrente) elevan por igual el riesgo cardiovascular entre los pacientes diabéticos.

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obesity, and (controlled or uncontrolled) hyperglycemia, as well as to evaluate the cardiovascular effects of linagliptin in patients with isolated or recurrent hypoglycemic events. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:92-101)

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Key words: Atherosclerosis. Diabetes complications. DPP-4i. Linagliptin. Metformin. Cardiovascular risk. Sulfonylurea.

El presente artículo tiene como objetivos: a) Evaluar la eficacia para el control glucémico y la seguridad de linagliptina (iDPP-4) en relación con su bajo potencial para ganancia de peso corporal y episodios de hipoglucemia. b) Presentar una revisión de la eficacia de linagliptina para el control de los factores de riesgo cardiovascular en pacientes con hipertensión arterial, obesidad e hiperglucemia (controlada o no controlada), al igual que los efectos cardiovasculares de linagliptina en pacientes afectados por eventos de hipoglucemia aislados o recurrentes.

Palabras clave: Aterosclerosis. Complicaciones de la diabetes. iDPP-4. Linagliptina. Metformina. Riesgo cardiovascular. Sulfonilureas.

INTRODUCTION

Type 2 diabetes mellitus: individual and social impact around the world and in Mexico

Data published by the World Health Organisation (WHO) have shown that there are approximately 350 million people worldwide affected by type 2 diabetes mellitus (T2DM). Also according to this WHO report, more than 80% of deaths attributed directly to diabetic complications are occurring in low- and medium-income regions; in the analysis of mortality attributed to T2DM, approximately 50% refer to patients under 70 years of age, of whom 55% are women[1].

The International Diabetes Federation (IDF) Diabetes Atlas 2014 update has given not-so-worrying statistical information; around the world, one of every 12 persons is already diabetic, one of every two has not been diagnosed and is unaware of this disease, and each seven seconds one person dies due to diabetic complications[2].

In Mexico, T2DM is the main cause of death and the annual number of deaths caused by it widely exceeds those due to ischemic heart disease and stroke[3]. According to IDF-2014 records, the T2DM national prevalence for the Mexican population was 11.92% (more than 9 million persons between 20 and 79 years of age have T2DM, and more than 2.5 million, it is thought, are still undiagnosed). Even in 2014, more than 68,000 Mexicans patients died due to diabetic complications[2].

Analysis by group of age has revealed that T2DM primarily affects adults of productive age and elderly people in Mexico. Additionally, the T2DM prevalence is higher among patients with a family history (father, mother or both) of T2DM than those without that background (11.4 vs. 5.6%)[4].

Meanwhile, the highest T2DM prevalence occurs in the population with obesity (or abdominal obesity); a healthy diet, regular physical exercise, maintenance of normal body weight, and quitting smoking may prevent or delay T2DM[1,4].

Frequent comorbidities and complications

Based on the Mexican health surveys, a high percentage of T2DM patients are affected by other concomitant chronic diseases: 23.3% has hypercholesterolemia, 15.5% albuminuria (and its complications), 13.7% arterial hypertension, and 12.3% nephropathy[4].

Type 2 diabetes mellitus also causes chronic complications such as vascular disease, neuropathic syndromes, and mixed (both vascular and

Table 1. Frequent chronic complications in type 2 diabetes mellitus[5]

Vascular diseases	Macrovascular: Accelerated cerebrovascular -or coronary- atherosclerosis Accelerated peripheral vascular disease Microvascular: Diabetic nephropathy Diabetic retinopathy
Neuropathic syndromes	Autonomic neuropathy: Diabetic enteropathy Sexual dysfunction Diabetic gastroparesis Diabetic orthostatic hypertension Diabetic neurogenic bladder Sensitive-motor neuropathy: Diabetic amyotrophy Diabetic neuropathic cachexia Diabetic mononeuropathy Diabetic polyneuropathy (bilateral, symmetric, more in lower than upper extremities): pain, foot deformation, ulceration
Mixed (vascular and neuropathic) diseases	Ulcer in legs and feet

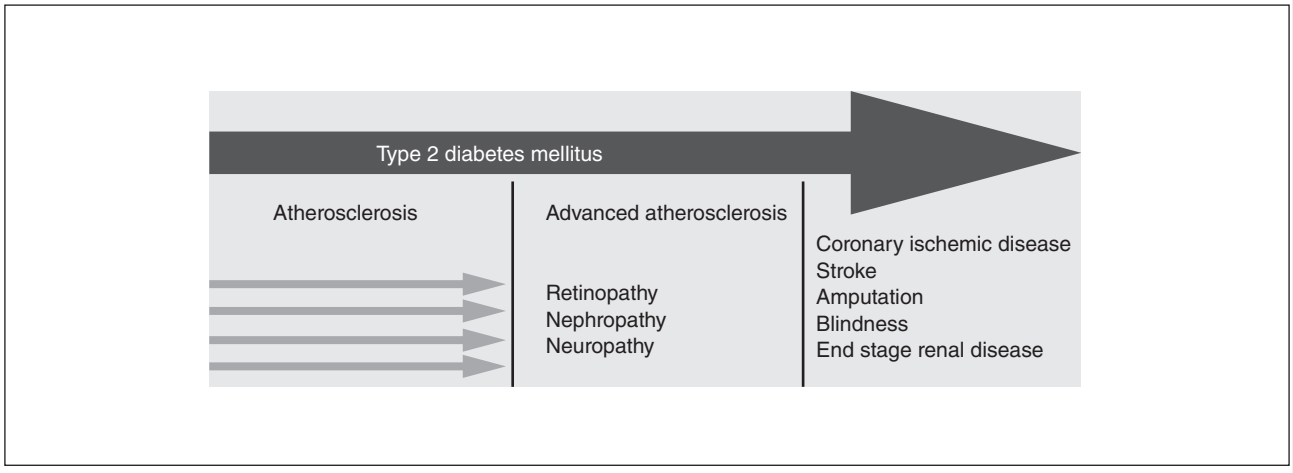

Figure 1. Type 2 diabetes mellitus, atherosclerosis, complications, and increased cardiovascular risk[6].

neuropathic diseases) diseases, including those shown in table 1[5].

Type 2 diabetes mellitus and increased cardiovascular risk

Type 2 diabetes mellitus is a progressive and chronic disease, promoting the development of several complications (diabetic nephropathy, neuropathy and retinopathy), where advanced atherosclerosis is not an uncommon finding, and T2DM increases cardiovascular risk such as coronary disease and stroke (Fig. 1)[6].

Cardiovascular risk is 2-4 fold higher in T2DM patients than in general population. Between 70 and 80% of total deaths are caused by cardiovascular complications associated to advanced atherosclerosis, which

Table 2. Primary cardiovascular risk factors in type 2 diabetes mellitus patients[5]

General factors	Dyslipidemia: ↑ LDL (↑non-HDL), ↑Tg, ↓HDL, ↑TC/HDL, ↑Apo B, ↑ of small and dense LDL, lipid particle accumulation
	Arterial hypertension
	Smoking
Factors inherent to T2DM	Hyperglycemia
	Lipoprotein glycation
	Increased oxidative stress
	Insulin resistance
	Hypercoagulable disorders
	Endothelial damage
	Chronic inflammation
	Microalbuminuria

T2DM: type 2 diabetes mellitus; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Tg: triglycerides; TC: total cholesterol; Apo B: apolipoprotein B.

also accounts for 75% of hospitalizations of T2DM patients. The primary factors for cardiovascular risk related to T2DM are shown in table 2[5,7].

Effectiveness, safety and tolerability of linagliptin for treatment of patients with type 2 diabetes mellitus

Linagliptin: chemical structure and overall therapeutic effects

Due to its chemical structure, linagliptin is a xanthine-based dipeptidyl peptidase-4 (DPP-4) inhibitor[8] not mimicking the DPP-4 molecule.

Due to its mechanism of action, linagliptin is a competitive and reversible DPP-4 inhibitor. When strong binding to DPP-4 occurs, linagliptin builds three hydrogen bonds between amine (piperidine ring) and acceptor groups on Glu205, Glu206, and Tyr662 residues; a fourth hydrogen bond is formed between carbonyl C-6 (within xanthine structure) and the amide chain of Tyr631 residue[8,9].

Due to these chemical processes, linagliptin substantially reduces the degradation of insulinotropic hormone glucagon-like peptide 1 (GLP-1), leading to a better glycemic control in T2DM patients. Both GLP-1 and gastric inhibitory polypeptide (GIP) are incretin hormones increasing insulin production (also release) by pancreatic b-cells and concurrently reducing glucagon secretion by pancreatic α-cells. Since linagliptin prolongs the effects of these hormones, as a net result it decreases glucose hepatic production and increases glucose-dependent insulin secretion (Fig. 2)[6,8].

Pharmacokinetics and pharmacodynamics

Linagliptin selectivity for DPP-4 is particularly high (10,000-fold over other dipeptidyl peptidases)[2,8,9]; along with this high selectivity, linagliptin inhibitory potency at half maximal inhibitory concentration(IC50) is significantly higher than the IC_{50} shown by other dipeptidyl peptidase 4 inhibitors (DPP-4i): i.e. 19-fold higher than sitagliptin, 24-fold higher than alogliptin, 50-fold higher than saxagliptin, and 62-fold higher than vildagliptin[9].

One single oral dose of linagliptin (2.5 to 600 mg) administered to healthy volunteers was related to a half-life (tmax) value between 0.7 and 3.0 hours. However, higher linagliptin regular doses are associated with higher tmax values: 70-80 hours for 5-50 mg doses and 128-184 hours for a 100 mg dose. These effects are equivalent for male healthy volunteers and T2DM patients when linagliptin is administered at 2.5, 5, and 10 mg doses; therefore, high

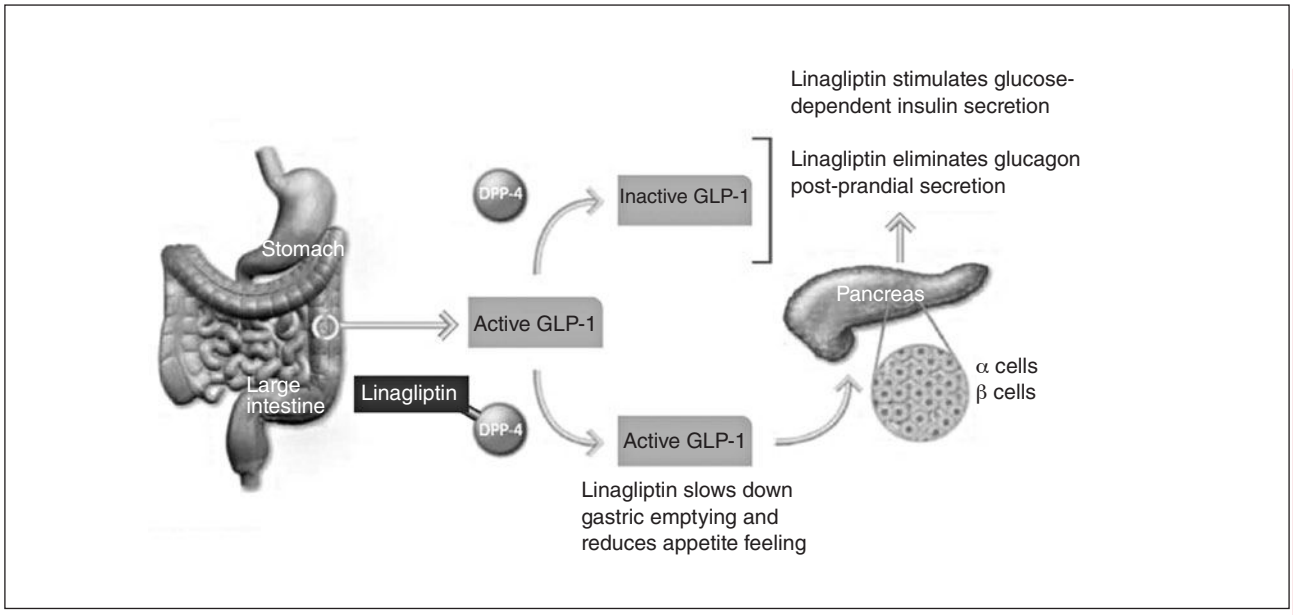

Figure 2. Dipeptidyl peptidase 4 enzyme inhibition by linagliptin and related physiological effects[6,8].
DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1.

tmax values related to daily oral doses cause a continuous DPP-4 inhibition, and the most effective tmax values for linagliptin are those related to linagliptin accumulation at 12 hours with 5 mg doses of this DPP-4i[8,9].

While linagliptin at 2.5 and 5 mg doses inhibits DPP-4 activity at rates of 72.7 and 86.1%, respectively, linagliptin at 5 and 10 mg doses inhibits DPP-4 by more than 90% in T2DM patients[8].

Clearance

Linagliptin clearance (primarily through fecal/enterohepatic route) makes this drug unique compared to other DPP-4i, because in all of them, clearance occurs primarily by the renal route. As the linagliptin primary clearance route is not renal, it could be administered in patients with renal failure without dose adjustment being required. A linagliptin 10 mg oral (PO) dose or a 5 mg intravenous (IV) dose has a fecal clearance of 84.7% (PO) and 58.2% (IV), and a non-significant renal clearance of 5.4% (PO) and 30.8% (IV)[8,10-12].

Delay of diabetes onset and β cell function preservation[13]

In a preclinical assay, female non-obese rats were fed either with a normal diet or one enriched with linagliptin 0.083 g/kg; the diabetes incidence decreased by up to 50% in animals treated with linagliptin ($p = 0.021$). Additionally, the total mass of islet cells and β cells was significantly higher in non-diabetic subjects receiving linagliptin ($p < 0.01$) than those without. The β-cell mass decreased substantially in diabetic subjects.

Effectiveness for glycemic control

Compared to placebo[10,14]:

- Treatment with linagliptin relates to a higher number of patients achieving a glycated hemoglobin target (HbA1c) of < 7.0% (18 vs. 10%).
- In a 12-week treatment, linagliptin reduces HbA1c by 0.60% in patients with baseline notable hyperglycemia (8.2 ± 1.0%; $p < 0.0001$; 95% confidence interval [95% CI]: −1.03 to −0.41).

– After 24 weeks of treatment with linagliptin, fasting plasma glucose values decreased by 15.5 mg/dl on average (95% CI: –29.6 to –1.3; p = 0.0323 for adjustment vs. placebo).

– A decrease of –0.72% (95% CI: –1.03 to –0.41; p < 0.0001) in HbA1c values occurred after a 52-week treatment with linagliptin.

– Linagliptin effectiveness for glycemic control is equivalent in patients with T2DM with or without concurrent renal failure.

Effects on body weight

For treatment-naive patients or those uncontrolled with other antidiabetic drugs, linagliptin induces harmless effects on body weight, comparable to those caused by placebo[15,16]:

– Treatment during 18 weeks with linagliptin was related to poorly significant body weight increase: 0.26 ± 0.33 kg with linagliptin vs. 0.09 ± 0.49 kg with placebo; i.e. placebo-adjusted change is only 0.17 kg (95% CI: –1.03 to 1.37; p = 0.7782).

– This effect has also been observed in a 24-week treatment with linagliptin: a 0.37 ± 0.15 kg increase with linagliptin vs. 0.21 ± 0.21 kg with placebo, for a placebo-adjusted change of only 0.16 kg (95% CI: –0.37 to 0.69; p = 0.5454).

Extra-glycemic effects

In assays in animals, it has been demonstrated that DPP-4i reduce the expression of reactive oxygen species (ROS) (1.07 ± 0.5 with DPP-4i vs. 4.6 ± 0.6 for controls; p < 0.0001) and the number of cells positive to 8-hydroxy deoxyguanosine (a product from DNA oxidation produced by ROS): 66.1 ± 4.5 cells for DPP-4i vs. 138.1 ± 7.4 for controls[17,18].

From this point of view, linagliptin has some almost exclusive pleiotropic effects uncommon to other DPP-4i, including its action on endotoxin-dependent activation of isolated leukocytes, its capacity to normalize the vascular impairment, and the reduction of oxidative stress and inflammation due to septic shock associated with lipopolysaccharides (LPS)[18].

In animal models of septic shock associated with LPS, the increase of ROS formation correlates to the expression of deleterious ROS for endothelial function. This is an indication of vascular damage. In one assay, LPS induced an increase in approximately 50% of the expression of ROS, and the use of linagliptin reduced this expression until its normalization. Thus, oxidative stress in vasculature (measured by dihydroethidium-dependent fluorescence microtomography, protein nitration, and malondialdehyde staining) decreased at the same time, therefore improving the endothelial function (p < 0.005 vs. controls)[18].

EFFECTIVENESS OF LINAGLIPTIN TO CONTROL CARDIOVASCULAR RISK FACTORS

Effects on hypertension

In T2DM patients, the primary factors that potentiate renal and cardiovascular risk are hypertension and microalbuminuria. A transitional pattern between microalbuminuria and chronic kidney disease has been clearly defined in clinical trials, as well as the continuous relation between albuminuria and increased mortality by cardiovascular causes. In addition, it has been demonstrated that changes in systolic and diastolic blood pressure were similar between linagliptin and placebo[19].

Meanwhile in essential hypertension, the relation between microalbuminuria and high blood pressure has parameters such as an increased systemic pressure towards the glomeruli and increased glomerular filtration, along with decreased albumin tubular reabsorption, and glomerular/arteriolar damage. These pathologies, which are mediated by an impaired fasting glucose, are present in T2DM patients, and they are aggravated by the

formation of ROS and an increase expression of proinflammatory cytokines and growth factors[20]. Therefore, screening for albuminuria is advised for this group at the time of diagnosis, and every 3-6 months[21].

In one study performed in 217 diabetic patients who were suffering diabetic nephropathy (urinary albumin-to-creatinine ratio [ACR] 30 to 3,000 mg/g), treatment with linagliptin substantially decreased the albuminuria. Higher ACR reductions were obtained than those associated with placebo (32 vs. 6%; p = 0.04)[22].

In a similar manner, a pooled analysis for four controlled studies with 217 patients with T2DM and albuminuria (ACR: 30 to 3,000 mg/g) showed the same pattern as commented above, and this was not influenced by either belonging to any race or HbA1c baseline values or systolic blood pressure values[23].

Effects in obese patients and/or metabolic syndrome patients

Studies in animal models for obesity and hepatic steatosis have shown that linagliptin treatment (3 or 30 mg/kg/day) for 3-4 weeks not only reduces HbA1c but also reduces the effect, improving sensitivity to hormone significantly ($p < 0.001$) compared with the vehicle-treated group. Through the DPP-4 inhibition, lower glucose levels are improved by glucose-dependent insulin secretion and reduced postprandial glucagon secretion, and it is possible that improved glycemia may reduce glucose toxicity associated insulin resistance and thereby increased insulin sensitivity[24].

The DPP-4i linagliptin, unlike management with other common drugs (including thiazolidinediones or insulin), which promote body weight gain, is suitable for long-term treatment as it preserves insulin secretion capacity by not affecting body weight and prevents progressive decline of β-cell function[25,26]. In a preclinical assay with female non-obese rats, the quantitative analyses of immunohistochemically stained islet cell types demonstrated a significantly higher β-cell mass in nondiabetic linagliptin-treated mice compared with nondiabetic vehicle (0.70 ± 0.093 vs. 0.35 ± 0.035 mg)[13].

Cardiovascular effects in patients with controlled or uncontrolled hyperglycemia

For both types of patients, treatment with linagliptin provides cardiovascular benefits derived from the following mechanisms.

As described in table 2, one of the primary factors for cardiovascular risk is hyperglycemia. According to this factor, the section "Effectiveness for glycemic control" establishes that linagliptin substantially improves glycemic control as it reduces HbA1c and fasting glucose to a worthwhile degree, and additionally, a recent meta-analysis suggested that using a gliptin in patients with T2DM was associated with a greater proportion of patients achieving their HbA1c goal of < 7%, without any weight gain or hypoglycemia[5,10,14].

Linagliptin increases endogenous GLP-1 concentrations and concurrently improves the lipid metabolism[27], which relates to the following effects:

- It improves endothelial function and attenuates renal and heart damage as a result of decreased proteinuria (from 128 ± 15 to 46 ± 7 mg/d) and albuminuria (from 86 ± 18 to 46 ± 7 mg/d)[28,29].
- In T2DM and stable coronary artery disease (CAD) patients, linagliptin produces remarkable vascular benefits: it increases brachial arterial diameter from baseline flow-mediated vasodilation (FMV) percentage (6.6 ± 1.0 vs. 3.1 ± 0.6% for controls; $p < 0.05$), without significant side effects on insulin sensitivity (4.5 ± 0.8 vs. 5.2 ± 0.9; p: ns); additionally linagliptin has a protecting effect on post-prandial endothelial function[28,30].
- Linagliptin protects the heart from ischemia or reperfusion damage by reducing infarct in a significant manner (up to 20.0 ± 2.8% with GLP-1 plus pyrrolidine valine [PV, added to prevent fast degradation of GLP-1] vs. 47.3 ±

4.3% with PV vs. 44.3 ± 2.4% with placebo; $p < 0.001$)[31].

– In ischemic heart segments, linagliptin primarily has the effect of protecting the heart from ischemia by improving left ventricular function (LVF) in patients with CAD: 77.0 ± 4.4 for ejection fraction vs. 70.8 ± 5.0% for controls ($p < 0.0001$); 12.18 ± 3.10 for mitral annular systolic velocity vs. 11.31 ± 3.11 cm/second for controls ($p = 0.0004$)[32].

Linagliptin not only acts on incretins in a favorable manner, but also on vasoactive peptides involved in inflammatory processes, immunity, and cardiovascular function. According to observations in preclinical trials, a decrease in DPP-4 activity (one of the crucial functions of linagliptin) reduces inflammation, stimulates endothelial repair, and attenuates ischemic damage[27]. A study in diabetic mice that were treated with linagliptin, obtained a reduction of cyclooxygenase-2 (proinflammatory marker) compared to the healthy mice ($p < 0.01$)[33].

Because linagliptin belongs to the xanthine group, it has some anti-oxidative properties and beneficial effects on vasculature[27]. In a study whose objective was to investigate the effect of linagliptin on beta-cell function and survival, human islets were exposed to diabetic milieu and linagliptin. It measured the nitro-tyrosine concentrations in islet, an indicator of oxidative stress, which were highly elevated under diabetic conditions but not in islets treated with linagliptin ($p < 0.05$)[34].

In studies comparing the cardiovascular effects of linagliptin vs. placebo vs. glimepiride or vs. voglibose, linagliptin has shown effectiveness in reducing the impact of events such as death from non-cardiovascular disease, non-fatal stroke, non-fatal myocardial infarct, and hospitalization due to unstable angina (relative risk [RR] vs. comparators of 0.34; 95% CI: 0.16-0.70)[35].

When linagliptin is directly compared to glimepiride, linagliptin is effective for glycemic control in patients poorly controlled with metformin monotherapy, without a risk factor for hypoglycemia or body weight gain. Additionally, it reduces cardiovascular risk vs. glimepiride; major cardiovascular events occurred in 12 out of 776 patients treated with linagliptin in the reference study (26 of 775 managed with glimepiride). That data involved a RR decrease for these events favoring linagliptin (–0.46; 95% CI: 0.23-0.91). Additionally, linagliptin treatment is superior to management with glimepiride in decreasing non-fatal stroke, regardless of glycemic condition: 26 patients experienced this event with glimepiride and only 12 with linagliptin (RR: 00.46; 95% CI: 0.23-0.91; $p = 0.0213$)[27,36].

Cardiovascular effects on patients affected by isolated or recurrent, controlled or uncontrolled hypoglycemia events

In clinical trials, linagliptin has shown effectiveness for glycemic control comparable to metformin or sulfonylureas, although linagliptin has a higher safety profile not only for harmless effects on body weight or low risk for hypoglycemia episodes, but also for its cardiovascular benefits greatly derived from its low risk for hypoglycemia and from the fact that dose titration is unnecessary, unlike other antidiabetic agents[27].

Some specialists claim that recurrent hypoglycemia or isolated hypoglycemia events are only markers for increased cardiovascular risk rather than causal mechanisms of cardiovascular morbidity and mortality in T2DM patients. The fact is that tight glycemic control may increase hypoglycemia incidence, and hypoglycemia correlates to major cardiovascular risk in clinical trials[37].

In six recent studies, the critical importance of understanding the relation between hypoglycemia and cardiovascular risk has been emphasized. Another 88 studies have concluded that hypoglycemia leads to increased cardiovascular risk by potentiating the thrombotic trend, disturbs heart repolarization, causes inflammation, and actively contributes to atherosclerosis development. Usually, these effects attributable to hypoglycemia lead to events such as unstable angina, fatal and non-fatal myocardial infarct, sudden death, and stroke[38].

Overall, hypoglycemia incidence is low with linagliptin use compared to placebo: 17.4 vs. 21% in some series. In other studies with Hispanic and Latin subjects, this incidence was only 10.1 vs. 19.4%, respectively, in patients receiving linagliptin without concurrent intake of a sulfonylurea[16].

CONCLUSIONS

Type 2 diabetes mellitus is a progressive and chronic disease that accelerates atherosclerosis, and it promotes the development of several complications with an increased cardiovascular risk.

Linagliptin clearance (primarily by fecal/enterohepatic route and in a very much lower manner by renal route) makes it a unique feature compared to the other DPP-4i with a clearance primarily by the renal route.

As the linagliptin primary clearance route is non-renal, it may be administered in patients with chronic renal failure without a dose adjustment being required.

In subjects studied in preclinical trials, linagliptin had a wide potential to delay diabetes onset and to preserve β-cell mass and function.

In treatment-naive patients or those non-controlled with other antidiabetic drugs, linagliptin induces harmless effects on body weight comparable to those caused by placebo.

Linagliptin is suitable for long-term treatment as it prevents β-cell progressive decline, preserving their insulin secretory capacity and not affecting body weight.

Linagliptin has some almost exclusive pleiotropic effects, generally not found with other DPP-4i, including its endotoxin-dependent action on isolated leukocytes and its capacity to normalize vascular damage and to reduce oxidative stress, as well as to reduce inflammation due to septic shock associated with lipopolysaccharides.

Linagliptin has a high effectiveness in glycemic control in patients with high cardiovascular risk since linagliptin treatment has a low impact on hypertension.

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