Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 36–39

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Dipeptidyl peptidase-4 inhibitors: Anti-diabetic drugs with potential effects on cancer

Alaa G. Almagthali [a], Eman H. Alkhaldi [a], Afnan S. Alzahrani [a], Ameera K. Alghamdi [a], Waleed Y. Alghamdi [a], Ahmed M. Kabel [b, c, *]

[a] Pharm D, College of Pharmacy, Taif University, Taif, Saudi Arabia
[b] Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[c] Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt

ARTICLE INFO

Article history:
Received 15 July 2018
Accepted 9 August 2018

Keywords:
Dipeptidyl peptidase-4 inhibitors
Diabetes mellitus
Cancer
Patients

ABSTRACT

Dipeptidyl peptidase (DPP- 4) inhibitors belong to the oral antidiabetic drugs. They are used for the treatment of Type 2 Diabetes mellitus. DPP-4 is an enzyme which puts down the action of hormone, incretin. Incretins belong to the group of hypoglycaemic gastrointestinal hormones. Some studies show that DPP-4 inhibitors causes cancer and some study show that they have anticancer property. This review sheds light on the role of the different types of DPP-4 inhibitors in cancer therapy.

1. Introduction

Type 2 diabetes is a chronic progressive condition in which the body becomes resistant to the normal effects of insulin, and ongoing decline in beta cell function, glucose levels likely will worsen over time [1]. Current pharmacologic treatments for type 2 diabetes are based upon suppressing hepatic glucose output, stimulating insulin release, mitigating glucose absorption, and increasing peripheral glucose utilization. Glucagon-like peptide-1 (GLP-1)-based therapies (e.g. dipeptidyl peptidase 4 [DPP-4] inhibitors, GLP-1 receptor agonists) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake [2].

DPP-4 inhibitors are a class of oral diabetes drugs that inhibit the enzyme DPP-4. DPP-4 is a ubiquitous enzyme expressed on the surface of most cell types that deactivates a variety of other bioactive peptides, including glucose-dependent insulinotropic polypeptide (GIP) and GLP-1; therefore, its inhibition could potentially affect glucose regulation through multiple effects. However, DPP-4 inhibitors have a modest effect on GLP-1 levels, compared with giving GLP-1 agonists. In clinical practice they are associated with significant reductions in HbA1c, no weight gain and a low risk of hypoglycaemia [2].

Sitagliptin was the first selective inhibitor of DPP-4, followed by vildagliptin, saxagliptin, linagliptin and, most recently, alogliptin. Sitagliptin is available as 25, 50, and 100 mg tablets. A sitagliptin/metformin combination was approved in April 2007 in tablet strengths of 50 mg/500 mg and 50 mg/1000 mg, respectively. Saxagliptin tablets, approved in July 2009, are sold in strengths of 2.5 and 5 mg. Both agents have been used as monotherapy and in combination with other antidiabetic drugs to help patients achieve blood glucose goals [3].

There are now extensive literature and multiple publications concerning the efficacy and general safety of the first three DPP-4 inhibitors: sitagliptin, vildagliptin and saxagliptin. These have been pulled together in a useful meta-analysis by Monami and colleagues, published in 2010. In the meta-analysis they included 32 published trials and nine unpublished trials with a duration greater than 12 weeks. They confirmed that, compared with placebo, the DPP-4 inhibitors reduced HbA1c by around 0.7%. The efficacy was similar in monotherapy and in combination with other agents. When comparisons were made with other oral drugs used in type 2 diabetes, the reductions in HbA1c were comparable with glitazones, but slightly less than with metformin or sulphonylureas. There was no weight gain and a very low risk of hypoglycaemia [4].

* Corresponding author. Department of Clinical Pharmacy, College of Pharmacy, Taif University, Al-Haweiah, P.O. Box 888, 21974, Saudi Arabia.
E-mail address: ahmed.kabal@med.tanta.edu.eg (A.M. Kabel).

https://doi.org/10.1016/j.dsx.2018.08.012
1871-4021/

2. Dipeptidyl peptidase enzyme and its role in growth of cancer

Dipeptidyl peptidase-4 (DPP4) or adenosine deaminasecomplexing protein 2 (ADCP 2) or T-cell activation antigen CD26 is a serine exopeptidase belonging to the S9B protein family that cleaves X-proline dipeptides from the N-terminus of polypeptides, such as chemokines, neuropeptides, and peptide hormones. The enzyme is a type II transmembrane glycoprotein, expressed on the surface of many cell types, whose physiological functions are largely unknown [5].

It is possible that the pleiotropic effects of CD26/DPPIV depends on its varied roles in differentcancers. Among its key characteristic are the ability to contribute with other key molecules and its cleavage of biological factors to regulate their functions. For example, it binds to plasminogen 2-epsilon, eliciting an intracellular [Ca2+] flux which leads to secretion/activation of MMP- 9 in 1-LN cells. It can also form heterodimers with FAP-alpha, colocalizing at pseudopodia and thus causing secretion/activation of MMPs in migratory fibroblasts and endothelial cells [6].Both of these activities indicate that CD26/DPPIV is involved in tumor metastasis. Nevertheless, its ability to bind fibronectin and collagen not only predicts a potential role in invasion, but also possibly an inability to migrate due to tight cell-cell adhesions mediated by CD26/DPPIV, as in the case for melanoma cells. Breaking of cytokines and chemokines by CD26/DPPIV also allows it to act as either a tumor suppressor or promoter. For example, SDF-1-alpha is one of the best CD26/DPPIV substrates in vitro, but whether it contributes significantly to the metabolism of SDF-1- alpha *in vivo* needs to be analyzed more. While many bioactive peptides are qualified to be CD26/DPPIV substrates, substrate recognition and breaking ability are probably regulated at least partly by the proteins associated with CD26/DPPIV and the tumor-specific microenvironment, which can modulate substrate binding ability to the enzyme active site. The local concentration of the putative substrate is also important for its interaction with CD26/DPPIV. Hence, the specific biological functions of CD26/DPPIV are likely to differ depending on its site, tumor cell type, oligomeric state, and the concentration of ligands and cofactors. In addition, multiple isoforms exist for both soluble and membrane-associated CD26/DPPIV, factors which add another layer of complexity to the role of this multifaceted molecule in tumor biology. In the meantime, its various functions in tumor development would indicate that CD26 may be an appropriate novel target for cancer therapy. For sure, our studies, as well as work done by others, suggest that targeting CD26/DPPIV with specific agents may be an effective therapy for selected cancers, which would be logical in view of the key role CD26/DPPIV plays in cancer biology [7].

3. Role of DPP_4 inhibitors in increasing immunity against tumors

In a new study entitled “Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and immunotherapy” researchers showed that inhibiting an enzyme Dipeptidylpeptidase 4 (DPP4) responsible for the degradation of key immune signals, increases the number of immune cells within the tumor microenvironment, leading to an efficient anti-tumoral response.

The success of antitumor immune responses depends on the infiltration of solid tumors by effector T cells, a process guided by chemokines. Chemokines are low-molecular-weight proteins secreted by cells that guide T cells towards tumors. However, these molecules can be degraded by enzymes, halting T cell infiltration and consequently tumor destruction by the immune system. One of these enzymes, dipeptidylpeptidase 4 (DPP4), degrades the chemokine CXCL10 responsible for targeting T cells into diseased tissues.

In this study, researchers showed that inhibiting the activity of DPP4 improves the immune efficacy, particularly against tumors. The team confirmed that DPP4 activity *in vivo* limited immune cells' migration towards tumors and other inflammatory locations within the body. Upon inhibition of DPP4 activity in mice, using a specific DPP4 inhibitor – sitagliptin, researchers observed that blocking this enzyme preserved the biological activity of the CXCL10 chemokine, resulting in an increase of the respective T cells into the tumor environment, therefore inhibiting tumor growth. Furthermore, the team showed DPP4 inhibition combined with other forms of immunotherapy (adjuvant-based immunotherapy, adoptive T cell transfer and checkpoint blockade) led to an increased efficiency of the overall immune response [8].

4. Potential role of DPP_4 inhibitors in treatment of cancer colon

Colorectal cancer is cancer that starts in the colon or rectum. These cancers can also be named colon cancer or rectal cancer, depending on where they start. Colon cancer and rectal cancer are often grouped together because they have many features in common [9]. Colorectal cancer is a leading cause of morbidity and mortality in industrialized countries worldwide [10].

Currently, most of the drugs used in the treatment of cancer are conventional cytostatic drugs and molecular targeted drugs acting on various oncogenic kinases such as KIT, KDR, RAS, MEK or members of the EGF receptor (R) family [11–16]. Targeted drugs, including EGFR/ErbB blockers, have also been applied in combination with chemotherapy [12,15,17]. However, resistance against one or more drugs is still a challenge in the treatment of colon cancer patients, and the same holds true for other solid tumors. In colorectal cancer, the molecular mechanisms of resistance to anti-EGFR therapies are complex and are considered to be associated with mutations and hyperactivation of pro-oncogenic downstream effector molecules such as KRAS, BRAF or PIK3CA, or with inactivating mutations in tumor suppressor genes like PTEN. Patients lacking mutations in pro-oncogenic genes have a higher probability to respond to EGFR-targeted therapy [18].

Colon cancer and insulin resistance (IR), a metabolic deregulation predisposing to Type 2 diabetes mellitus (T2DM), are affected by similar diet and lifestyle factors (*e.g.,* calorie-rich food and body and abdominal fatness together with low physical activity). Interestingly, both IR and T2DM patients are at increased risk of colon cancer [19].

Many antidiabetic drugs like metformin and Peroxisome proliferator-activated receptor gamma agonists have shown significant anticancer properties in cancer cells. Some studies show that DPP-4 inhibitors causes cancer and some study show that they have anticancer property [20].

In October 2006, the labeling for sitagliptin (Januvia), a DPP4 inhibitor, was approved by FDA for the treatment of type 2 diabetes mellitus [21]. Studies have shown that when Sitagliptin is given chronically at therapeutic range, it decreases colon cancer in rats. Sitagliptin also has cardio protective effects in mice and it has also shown improvement in Ischemic heart diseases [22,23].

Vildagliptin is another oral antidiabetic drug of the DPP-4 inhibitors family. By inhibiting DPP4, vildagliptin causes an increase in glucagon like peptide-1 (GLP-1), an intestinal hormone that aids in glucose homeostasis and insulin secretion [24].Vildagliptin is very effective in type II diabetes mellitus. Many studies have proved that it promotes the function of pancreas and maintains blood glucose levels [25], protects against vascular diseases by promoting

endothelial cell network formation and revascularization [26]. It has a protective role in hyperlipidaemia and has anti-inflammatory properties also [27].

In a new study conducted by C.A Amritha, PunnagaiKumaravelu and D. Darling Chellathai finds the anticancer activity as measured by the MTT method showed that Sitagliptin and Vildagliptin had anticancer activity. Percentage inhibition of Sitagliptin is more than Vildagliptin, in colon cancer cell lines. This significant anticancer activity of DPP-4 inhibitors could play a role as a cytotoxic agent in many tumour conditions [20].

5. DPP_4 inhibitors and the risk of development of pancreatic cancer

Dipeptidyl-peptidase-4 inhibitors (DPP-4i) have been implicated with an increased pancreatic cancer risk. In 2011, an analysis of the FDA Adverse Events Reporting System (FAERS) demonstrated increased rates of pancreatitis and pancreatic cancer with incretin-mimetics compared to other antihyperglycemic therapies. Pancreatic cancer rate with sitagliptin was found to be 2.7 times the rate in the control group, raising concern about a potential adverse effect [28].

The FAERS analysis has been criticized mainly due to the limitations of the FAERS database; including the lack of denominator, disproportionate reporting, confounding and inconsistencies in exposure and outcome ascertainment [29,30]. In March 2013, Butler et al. [31]examined pancreata from brain-dead organ donors and found increased pancreatic mass, exocrine cell proliferation and dysplasia in organ donors treated with incretin-mimetics (7 sitagliptin, 1 exenatide) compared with diabetic patients on other antihyperglycemic agents and non-diabetic controls. The authors suggested that these observations are compatible with an increased pancreatic cancer risk in those treated with incretin-mimetics [31]. However, this study is limited by small numbers ($n = 34$), poor matching on baseline characteristics and absence of information about treatment duration [32]. Following this, the FDA issued a drug safety communication announcing that it is evaluating such reports but that it had “not reached any new conclusions about safety risks with incretin-mimetics” [33].Recently two trials (SAVOR-TIMI 53 and EXAMINE) evaluating the cardiovascular effects of DPP-4i were reported [34,35]. The SAVOR-TIMI compared saxagliptin versus placebo over median 2.1 years follow-up and evaluated pancreatic cancer as a safety outcome but found no indication for an increased risk (5 events with saxagliptin versus 12 with placebo) [34]. The EXAMINE trial comparing alogliptin versus placebo found no reports of pancreatic cancer over about 1.5 years of median follow-up in 5380 patients [35].

6. Conclusion

Dipeptidyl peptidase (DPP)-4 is a multifunctional cell surface protein that is widely expressed in most cell types including T lymphocytes, on which it is a marker of activation. Dipeptidyl peptidase (DPP)-4 inhibitors belong to one class of drugs that have been approved for treatment of type 2 diabetes (T2D) based on the glucose-lowering actions of the gastrointestinal hormone glucagon-like peptide (GLP)-1. Inhibiting an enzyme Dipeptidylpeptidase 4 (DPP4) responsible for the degradation of key immune signals, increases the number of immune cells within the tumor microenvironment, leading to an efficient anti-tumoral response.

Conflicts of interest

The authors had no conflict of interest to declare.

References

[1] Kabel AM. Zinc/alogliptin combination attenuates testicular toxicity induced by doxorubicin in rats: role of oxidative stress, apoptosis and TGF-β1/NF-κB signaling. Biomed Pharmacother 2018;97:439–49.
[2] Kabel AM, Omar MS, Alhadhrami A, Alharthi SS, Alrobaian MM. Linagliptin potentiates the effect of l-dopa on the behavioural, biochemical and immunohistochemical changes in experimentally-induced Parkinsonism: role of toll-like receptor 4, TGF-β1, NF-κB and glucagon-like peptide 1. Physiol Behav 2018;188:108–18.
[3] Pathak R, Bridgeman MB. Dipeptidyl Peptidase-4 (DPP-4) inhibitors in the management of diabetes. Int. J. Pharm. Therapeut. 2010;35(9):509–13.
[4] Monami M, Iacomelli I, Marchionni N, Mannucci E. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metabol Cardiovasc Dis 2010;20:224–35.
[5] Matteucci E, Giampietro O. Dipeptidyl peptidase-4 (CD26): knowing the function before inhibiting the enzyme. Curr Med Chem 2009;16(23):2943–51.
[6] Ghersi G, Zhao Q, Salamone M, Yeh Y, Zucker S, Chen WT. The protease complex consisting of dipeptidylpeptidase IV and Seprase plays a role in the migration and invasion of human endothelial cells in collagenous matrices. Canc Res 2006;66:4652–61.
[7] Havre Pamela A, Abe Masako, Urasaki Yasuyo, Ohnuma Kei, Morimoto Chikao, Nam H, Dang. The role of CD26/dipeptidyl peptidase IV in cancer. Front Biosci 2008;13:1634–45.
[8] Barreira da Silva R, Laird ME, Yatim N, Fiette L, Ingersoll MA, Albert ML. Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and immunotherapy. Nat Immunol 2015;16(8):850–8.
[9] Kabel AM, Atef A, Estfanous RS. Ameliorative potential of sitagliptin and/or resveratrol on experimentally-induced clear cell renal cell carcinoma. Biomed Pharmacother 2018;97:667–74.
[10] Grunt TW, Hebar A, Laffer S, Wagner R, Peter B, Herrmann H, et al. Prominin-1 (CD133, AC133) and dipeptidyl-peptidase IV (CD26) are indicators of infinitive growth in colon cancer cells. Am J Cancer Res 2015;5(2):560–74.
[11] Reidy D, Saltz L. Targeted strategies in the treatment of metastatic colon cancer. J Natl Compr Canc Netw 2007;5:983–90.
[12] Linardou H, Dahabreh IJ, Kanaloupiti D, Siannis F, Bafaloukos D, Kosmidis P, Papadimitriou CA, Murray S. Assessment of somatic KRAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncol 2008;9:962–72.
[13] Grothey A, Galanis E. Targeting angiogenesis: progress with anti-VEGF treatment with large molecules. Nat Rev Clin Oncol 2009;6:507–18.
[14] Köhne CH, Lenz HJ. Chemotherapy with targeted agents for the treatment of metastatic colorectal cancer. Oncol 2009;14:478–88.
[15] Cohen DJ, Hochster HS. Update on clinical data with regimens inhibiting angiogenesis and epidermal growth factor receptor for patients with newly diagnosed metastatic colorectal cancer. Clin Colorectal Canc 2007;7(Suppl 1): S21–7.
[16] Yamatodani T, Ekblad L, Kjellen E, Johnsson A, Mineta H, Wennerberg J. Epidermal growth factor receptor status and persistent activation of Akt and p44/42 MAPK pathways correlate with the effect of cetuximab in head and neck and colon cancer cell lines. J Canc Res Clin Oncol 2009;135:395–402.
[17] Jiang Y, Kimchi ET, Staveley-O'Carroll KF, Cheng H, Ajani JA. Assessment of KRAS mutation: a step toward personalized medicine for patients with colorectal cancer. Cancer 2009;115:3609–17.
[18] Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. J Clin Oncol 2010;28:1254–61.
[19] Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–85.
[20] Amritha CA, Kumaravelu Punnagai, Darling Chellathai D. Evaluation of anti cancer effects of Dpp-4 inhibitors in colon cancer- an invitro study. J Clin Diagn Res 2015 Dec;9(12):FC14–6.
[21] Kabel AM, Al-Shehri AH, Al-Talhi RA, Abd Elmaaboud MA. The promising effect of linagliptin and/or indole-3-carbinol on experimentally-induced polycystic ovarian syndrome. Chem Biol Interact 2017;273:190–9.
[22] Ye Y, Keyes KT, Zhang C, Perez-Polo JR, Lin Y, Birnbaum Y. The myocardial] infarct size-limiting effect of sitagliptin is PKA dependent, whereas the protective effect of pioglitazone is partially dependent on PKA. Am J Physiol Heart Circ Physiol 2010;298:H1454–65.
[23] Read P, Khan F, Heck P, et al. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigate stunning in a pilot study of patients with coronary artery disease. CircCardiovascImag 2010;3: 195–201.
[24] Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 2005;90:4888–94.
[25] Akarte AS, Srinivasan BP, Gandhi S. Vildagliptin selectively ameliorates GLP-1, GLUT4, SREBP-1c mRNA levels and stimulates β-cell proliferation resulting in improved glucose homeostasis in rats with streptozotocin-induced diabetes. J Diabet Complicat 2012;26(4):266–74.
[26] Kröller-Schön S, Knorr M, Hausding M, Oelze M, Schuff A, Schell R. Glucoseindependent improvement of vascular dysfunction in experimental sepsis by dipeptidyl-peptidase 4 inhibition. Cardiovasc Res 2012;96(1):140–9.

[27] Inaba W, Mizukami H, Kamata K, Takahashi K, Tsuboi K, Yagihashi S. Effects of long-term treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin on islet endocrine cells in non-obese type 2 diabetic Goto-Kakizaki rats. Eur J Pharmacol 2012;691(1–3):297–306. https://doi.org/10.1016/j.ejphar.2012.07.030. Epub 2012 Jul 20.
[28] Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011;141(1):150–6.
[29] FDA 2011 adverse event reporting System. [Accessed April 10, 2013]; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. 4-26-2013.
[30] Drucker DJ, Sherman SI, Bergenstal RM, et al. The safety of incretin-based therapies–review of the scientific evidence. J ClinEndocrinolMetab 2011;96(7):2027–31.
[31] Butler AE, Campbell-Thompson M, Gurlo T, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013 Jul;62(7):2595–604.
[32] Kahn SE. Incretin therapy and islet pathology - a time for caution. Diabetes 2013 Jul;62(7):2178–80.
[33] FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes. [Accessed April 20th, 2013];http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm344232.htm.
[34] Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013 Oct 3;369(14):1317–26.
[35] White William B, Cannon Christopher P, Heller Simon R. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.