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Incretin-Based Therapies and Cancer Risk: A Review of Recent Literature Safety Data

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Abstract

Type 2 diabetes mellitus represents almost 90–95% of all diabetes. In 2006 and in 2007, the pharmacological treatment of type 2 diabetes mellitus changed due to the introduction on the European market of the first GLP-1 receptor agonist, exenatide, and the first inhibitor of DPP-4, sitagliptin. These drugs act throughout the potentiation of incretin receptor signalling. Today, other 4 GLP-1 receptor agonists and DPP-4 inhibitors have obtained marketing approval. However as far as the safety of these drugs is concerned, some issues were recently raised regarding an increase in the risk of cancer. Therefore, in order to define the correlation between incretin-based therapies and the risk of cancer, a literature search was performed. Data was taken from recent pre-clinical and clinical studies in which tolerability of GLP-1 receptor agonists and DPP-4 inhibitors and was evaluated. In total, data obtained from 38 preclinical and clinical studies was analysed. It was evident from these studies that the risk of cancer associated to incretin-based therapies was very low. Results demonstrated that in more than 80,000 patients treated with these drugs, little over 60 cases of cancer were diagnosed. Moreover, results from EXAMINE and SAVOR-TIMI53 trials showed that the number of malignancies in patients treated with inhibitors of DPP-4 inhibitors was similar to number of cancer events occurring in patients in placebo groups. Data from pre-clinical studies also revealed encouraging results. Clearly, it is not a simple task to define the correlation between these drugs and the cancer risk especially as patients with type 2 diabetes already have a risk factor for cancer. According to the European Medicine Agency and Food and Drug Administration, it is important to continue monitoring the safety of patients treated with incretin-based therapies.

Keywords: T2DM; Incretin-based therapies; Cancer risk

Introduction

According to the International Diabetes Federation, today 387 million people have diabetes and by 2035 this number will grow to about 592 million [1]. Type 2 diabetes mellitus (T2DM) represents almost 90–95% of all diabetes. It includes patients with insulin resistance and relative insulin deficiency; moreover, a higher percentage of patients with T2DM are obese and obesity induces insulin resistance [2].

As several complications, such as micro- and macro-vascular disorders, derive from diabetes, it is important to treat the disease quickly. The first approach in the management of diabetes is represented by lifestyle modifications (weight control, physical activity, and dietary modification). When lifestyle modifications are insufficient, there is then a specific need to introduce medications to achieve treatment goals [3]. The aim is to target HbA1c below 7% in order to reduce the risk of end-organ damage [4]. When pharmacological therapy with metformin, the usual first choice of treatment, fails, other antidiabetic drugs can be used (sulfonylureas - SU, thiazolidinediones – TZD, glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 inhibitors [DPP-4i]). When used alone, these medications show an initial efficacy, but following this a worsening of glycaemic control due to a steady and progressive decline in pancreatic β-cell function is commonly associated. Most type 2 diabetic patients thus necessitate a combination of antidiabetic drugs. Finally, insulin therapy will be required by most patients [5].

In 2006 and in 2007, the pharmacological treatment of T2DM drastically changed thanks to the introduction on the European market of the first GLP-1 receptor agonist, exenatide, and the first DPP-4i, sitagliptin. These drugs obtained the marketing approval by Food and Drug Administration (FDA) in 2005 and 2006, respectively. These antidiabetic agents act throughout the potentiation of incretin receptor signalling. Specifically, incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, are gut hormones that enhance insulin secretion after meal ingestion. Incretin-based therapies potentiate incretin signalling throughout inhibition of DPP-4 enzyme, which operate the N-terminal cleavage and inactivation of GIP and GLP-1, and the agonist activity of GLP-1R, very similar to human GLP-1 [6]. Exenatide and sitagliptin are used in association with metformin or a SU or TZD in patients who are non-responders to other oral agents [7]. After the marketing approval of exenatide and sitagliptin, other 4 GLP-1 receptor agonists (liraglutide, lixisenatide, albiglutide, dulaglutide) and 4 DPP-4i obtained marketing approval in Europe (vildagliptin, saxagliptin, linagliptin, alogliptin).

Data regarding the efficacy of GLP-1 receptor agonists and DPP-4i showed that these drugs improve glycaemia control and also beta-cell function, blood pressure, and lipid levels [8,9]. Regarding safety, incretin-based therapies are associated with different adverse events that include infections, hypersensitivity reactions, effects on body

weight, lipid profile and blood pressure, pancreatitis and, finally, a risk of cancer [10-17].

With regard to the risk of pancreatitis, a cohort study evaluated the incidence rate and relative risks of acute pancreatitis and severe acute pancreatitis in 547,554 and 584,373 patients with and without diabetes. The study revealed that diabetes is associated with an increased risk of pancreatitis [18]. Some studies demonstrated a possible correlation between the incretin-based therapies and pancreatitis while others exclude this risk. In particular, as recently reported by Singh et al., the risk of pancreatitis in 1269 hospitalized patients treated with sitagliptin and exenatide was twofold compared with 1269 non-users of incretins [19]. On the contrary, numerous meta-analyses of clinical trials [20,21] and independent retrospective studies [22-25] did not reveal any correlation between the risk of pancreatitis and incretin-based therapy.

In recent years, some concerns were raised regarding an increase in the risk of cancer. Data obtained from pre-clinical studies showed that GLP-1 activation stimulates the development of C-cell hyperplasia and medullary thyroid carcinoma [26]. Very similarly, in animal models, the DPP-4 inhibition is associated with the onset of melanoma, prostatic, pulmonary, and ovarian cancer [27-29]. On the contrary, a meta-analysis of 25 clinical trials revealed that exenatide and liraglutide are not associated with an increased risk of thyroid cancer [30]. The risk of pancreatic and thyroid cancers associated with incretin-based therapies was evaluated in a study which examined the FDA's database of reported adverse events (in the period 2004-2009) where sitagliptin and exenatide were reported as suspected drugs. Compared to patients treated with other therapies (rosiglitazone, nateglinide, repaglinide, and glipizide), the ones who took sitagliptin or exenatide presented pancreatic cancer more commonly. In particular, the reported rate of pancreatic cancer was 2.9-fold greater and 2.7-fold greater in patients treated with exenatide and sitagliptin, respectively, compared to rosiglitazone ($p=9 \times 10-5$; $p=0.008$). Moreover, authors observed an increase in the occurrence of thyroid cancer in patients treated with exenatide (OR = 4.73; $p=4 \times 10-3$). This increase was not seen in the sitagliptin group (OR=1.48; p=0.65). Finally, regarding all the other types of cancers, neither sitagliptin nor exenatide were associated with a higher reported rate of other forms of cancers [31].

In the light of available data, it is not possible to define the specific cause of cancer in patients with T2DM. Therefore, in order to define the correlation between incretin-based therapies and the risk of cancer, an extensive literature search analysing data from recent pre-clinical and clinical studies was performed. Tolerability of GLP-1 receptor agonists and DPP-4i was evaluated. Firstly, the biological role of T2DM in the development of malignant disease will be discussed.

T2DM and Cancer Risk

Current epidemiologic evidence reveal that patients affected by T2DM and obesity have a significantly higher risk to develop several forms of cancer, including breast, bladder, endometrial, hepatic, pancreatic and pulmonary cancers. The biological mechanisms underlying the association between diabetes and cancer are still unclear, but several conditions, such as insulin resistance, hyperinsulinemia, increased levels of Insulin Growth Factor (IGF), steroid and peptide hormones, and inflammatory markers, could play an important role in the onset of cancer [32]. According to Giovannucci et al., insulin and IGF influence several mechanisms of proliferation and apoptosis and consequently may induce carcinogenesis [33]. In particular, insulin and IGF, which bind four types of receptor (INS-R-A, INS-R-B, IGF-1-R and hybrid receptors), share metabolic and mitogenic pathways. Specifically, the binding to INS-R-A, IGF-1-R and hybrid receptors lead to different mitogenic effects that include increase in cell proliferation, inhibition of apoptosis, angiogenesis and cell migration [27].

In addition to the direct effects of insulin, T2DM can increases other pathways resulting in cancer progression. In fact, all factors produced by adipose tissue, such as free fatty acids, interleukin-6 (IL-6), monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1), adiponectin, leptin, and tumor necrosis factor-α are linked to cancer transformation or progression [34].

Harding et al. [35] assessed the excess risk of cancer incidence and mortality in patients with type 1 diabetes and T2DM compared with the general Australian population using data from a national diabetes and cancer registries. The study involved a total of 953,382 patients, of which 80,676 with type 1 diabetes and 872,706 with T2DM. As revealed by results, in patients with T2DM the incidence and mortality ratios (SIRs/SMRs) are significantly higher for all site-specific cancers. In particular, the highest SIRs were found for both liver and pancreas, while significant SMRs were observed for liver, pancreas, kidney, Hodgkin's lymphoma, gallbladder, stomach, and non-Hodgkin's lymphoma [35]. Similar data was also published in a comprehensive assessment of the risk of cancer in a nationwide cohort of diabetics in Denmark. Results confirmed that patients with a diagnosis of diabetes are at higher risk of developing hepatic, biliary tract, pancreatic, endometrial, and renal cancers [36]. Moreover, since adipocytes increase the inflammatory process throughout the release of adipokines, leptin, IL-6, TNF-α and VEGF, obesity is also associated with an increased risk of cancer [37]. Furthermore, the same pancreatitis, frequently associated to diabetes and diabetes therapies, is a known risk factor for pancreatic cancer (Table 1) [38,39].

Authors/study characteristics	Results	Reference
de Heer et al./ Review of literature	The binding of insulin to receptors, such as INS-R-A, IGF-1-R and hybrid receptors, leads to an increase in cell proliferation, inhibition of apoptosis, angiogenesis and cell migration.	[27]
Cohen et al./ Review of epidemiological evidence and literature	Insulin resistance, hyperinsulinemia, increased levels of insulin growth factor (IGF), steroid and peptide hormones, and inflammatory markers could play an important role in the onset of cancer events.	[32]
Giovannucci / Review of literature	Insulin and IGF influence several mechanisms of proliferation and apoptosis and consequently may induce carcinogenesis. Moreover, in animal studies hyperinsulinemia enhances colon carcinogenesis.	[33]

Giovannucci et al./ Consensus statement of experts assembled jointly by the American Diabetes Association and the American Cancer Society	Type 2 diabetes and obesity can increase pathways which result in malignant progression.	[34]
Harding et al./ Analysis of data from a national diabetes and cancer registries.	Incidence and mortality ratios (SIRs/SMRs) are significant high for all site-specific cancers in patients with type 2 diabetes.	[35]
Wideroff et al./ Analysis of data from the Danish Central Hospital Discharge Register	Higher risk of hepatic, biliary tract, pancreatic, endometrial, and renal cancers in diabetic patients were observed.	[36]
Prieto-Hontoria et al./ Review of literature	There is a strong association between obesity and breast, esophageal, colorectal and other types of cancer.	[37]
Whitcomb et al. and Brand et al./ Review articles	Chronic pancreatitis could predispose to pancreatic cancer. Results of several studies revealed that patients with chronic pancreatitis have a 4-14-fold increased pancreatic cancer risk.	[38,39]

Table 1: Summary of papers describing the association between type 2 diabetes, obesity, pancreatitis and cancer risk.

GLP-1 receptor agonists and cancer risk

Several studies have evaluated the safety profile of GLP-1 receptor agonists [40-58]. In particular, safety profile of exenatide, administered in a dosage of 2 mg/weekly or 20 μg/daily, was assessed in the DURATION-1 randomized clinical trial. Results showed that throughout the five years of treatment only one case of pancreatic cancer was detected [40]. Results of an analysis of individual 4,328 patient data from eight phase III trials of exenatide (six trials from the DURATION programme and two trials conducted in Asian populations), in which the safety profile of exenatide (once weekly or twice daily) was compared to liraglutide, sitagliptin, pioglitazone, metformin, and insulin glargine, showed that thyroid neoplasm was infrequently reported in treatment groups, while no cases of thyroid cancer or C-cell carcinoma were described. Only one case of pancreatic neoplasm was reported for exenatide administered twice daily and three cases of prostate cancer were reported for exenatide administered once weekly [41]. Exenatide demonstrated a good safety profile also in two pre-clinical studies [42,43]. In particular, the first study, which assessed the effects on development of intrahepatic cholangiocarcinoma of exenatide and oxaliplatin in vitro tests, suggested that the combination oxaliplatin/exenatide could reduce the proliferation of tumor cells and endorse apoptosis [42]. Moreover, as shown by Nomiyama et al. study, exenatide significantly reduced the proliferation of the prostate cancer cell lines LNCap, PC3, and DU145 and also decreased prostate cancer growth through the inhibition of ERK-MAPK activation [43].

Liraglutide was the second GLP-1 receptor agonist approved by EMA in 2009. The efficacy/safety profile of liraglutide associated to insulin degludec was compared in a phase 3 trial with the drugs given singularly in 1,663 insulin-naive patients. No cases of thyroid cancer were reported as safety results emerged [44]. When the safety profile of liraglutide was compared to placebo in 846 diabetic adults, frequencies of neoplasms were found to be similar in treatment groups (5 events in liraglutide group vs. 4 events in placebo group). Moreover, no cases of medullary thyroid carcinoma were identified in patients who received liraglutide, while one case was detected in the placebo group [45]. The association liraglutide/pancreatic cancer was evaluated in a post-marketing safety assessment programme using data from US commercial health insurance claims database and regarding patients treated with liraglutide, exenatide, metformin, pioglitazone or DPP-4i or SU. Results showed that the incidence rate (IR/100,000 person-years) for pancreatic cancer for liraglutide and all other therapies was 19.9 vs. 33.0, respectively (IR for pancreatic cancer for DPP-4 inhibitors, sitagliptin, saxagliptin, and linagliptin, was 37.1; SU, glyburide, glipizide and glimiperide, had the higher IR, equal to 52.9). In the light of the data analysed, no increased risk of pancreatic cancer in association with liraglutide was observed [46]. Lastly, the administration of liraglutide in patients with T2DM and dialysis-dependent end-stage renal disease (ESRD) or normal kidney function did not cause the occurrence of cancer events [47].

A good safety profile, in terms of cancer events, was also confirmed for lixisenatide, the third GLP-1 receptor agonist marketed. In fact, results of two studies [48,49], which evaluated the efficacy, safety and pharmacodynamic characteristics of the drug, revealed that the most common adverse events were gastrointestinal disorders and no data was reported regarding cancer events. Finally, additional information regarding pancreatic cancer related to lixisenatide will be obtained from the results of the randomized, double-blind, placebo-controlled, parallel-group, multicenter study ELIXA. This trial is evaluating the effects of lixisenatide in 6,068 patients at high CV risk [50].

Albiglutide and dulaglutide are two new GLP-1 receptor agonists approved in 2014. In HARMONY-1, a randomized, double-blind, placebo-controlled study, 310 patients already treated by pioglitazone were randomized to receive supplementary treatment with albiglutide or placebo. Data showed that no patient had thyroid cancer [51]. Similarly, Weissman et al. study confirmed the absence of thyroid cancer in 779 patients treated with the combined therapy albiglutide (once-weekly) and insulin glargine (once-daily) [52]. Lastly, the safety of albiglutide was recently compared to sitagliptin in patients with T2DM and renal impairment. Specifically, results of safety assessments revealed that a similar percentage of patients in albiglutide and sitagliptin groups had an adverse event (83.5% vs. 83.3%). Eight patients died during the study; of these, four patients treated with albiglutide died for pleural mesothelioma, pancreatic pseudocyst, sudden cardiac death, and cardiac disorder, while four in sitagliptin group died due to ischemic stroke, subarachnoid hemorrhage, malignant melanoma, and gastroenteritis [53].

Dulaglutide efficacy and safety were evaluated during the AWARD programme which consisted in a series of clinical trials. In particular, AWARD-1 enrolled patients with T2DM treated with metformin and pioglitazone, who were randomized to receive in double-blind dulaglutide 0.75 or 1.5 mg, and in open-label exenatide 20 μg/day or

placebo (double-blind). Patients who were treated with placebo were switched after 26 weeks to dulaglutide. As reported by safety results, in dulaglutide 1.5 mg group, one patient died of pancreatic cancer, while one patient had chronic pancreatitis [54]. In AWARD-2 and AWARD-3 trials, efficacy and safety of dulaglutide were compared to glargine insulin and metformin, respectively. As shown by safety results, the most common adverse events were gastrointestinal and nasopharyngitis. No cases of cancer were reported during the studies [55,56]. Similarly, no events of pancreatic cancer were noted in AWARD-4 trial [57]. Finally, results of AWARD-5 study, which compared the efficacy/safety profile of dulaglutide (1.5 or 0.75 mg) vs. sitagliptin 100 mg, showed that, in the period up to 104 weeks of treatment, there were 5 cases of neoplasm in dulaglutide 1.5 mg group, 3 in dulaglutide 0.75 mg group, and 5 in sitagliptin group [58]. Finally, a preclinical study has evaluated the carcinogenic effects of dulaglutide in rats and transgenic mice treated with dosage of study drug of 0, 0.05, 0.5, 1.5, or 5 mg/kg. Results revealed that while in rats there was a statistical increase in C-cell hyperplasia, adenomas and C-cell carcinomas at 0.5 mg/kg or greater, in transgenic mice at any dose dulaglutide did not induce C-cell hyperplasia or neoplasia (Table 2) [59].

Authors/study characteristics	Assessment and population	Cases of cancer detected	Reference
Wysham et al./RCT	Safety of exenatide in 153 patients who completed 5 years of treatment.	One case of pancreatic cancer.	[40]
Gough et al./ RCT	Efficacy/safety profile of liraglutide associated to insulin degludec compared with the drugs given alone in 1,663 insulin-naive patients.	No cases of thyroid cancer.	[44]
Davies et al./RCT	Safety profile of liraglutide compared to placebo in 846 patients.	Five cases of neoplasm in liraglutide group vs. four events in placebo group. One case of medullary thyroid carcinoma in placebo group.	[45]
Idorn et al./ RCT	Safety and efficacy of liraglutide in 20 patients with type 2 diabetes and ESRD and 20 patients type 2 diabetes and normal kidney function.	No cancer events were identified.	[47]
Seino et al./ RCT	Efficacy, safety and pharmacodynamics of lixisenatide in 120 diabetic patients.	No cancer events were reported.	[48]
Onishi et al./RCT	Efficacy and safety of lixisenatide in 127 diabetic patients.	No data were reported regarding to cancer events.	[49]
Reusch et al./ RCT	Efficacy and safety of albiglutide compared to placebo in 310 diabetic patients.	No cases of thyroid cancer.	[51]
Weissman et al./ RCT	Efficacy and safety of albiglutide with insulin glargine in 779 diabetic patients.	No cases of thyroid cancer.	[52]
Wysham et al./ RCT	Efficacy and safety of dulaglutide added to pioglitazone and metformin vs exenatide in 978 patients with type 2 diabetes.	One patient treated with dulaglutide died for pancreatic cancer.	[54]
Giorgino et al./ RCT	Efficacy and safety of once-weekly dulaglutide compared to daily insulin glargine in 810 patients with type 2 diabetes.	No cases of cancer were detected.	[55]
Umpierrez et al./ RCT	Efficacy and safety of monotherapy with dulaglutide compared to metformin-treated in 807 patients with type 2 diabetes.	No cases of cancer were detected.	[56]
Blonde et al./ RCT	Efficacy and safety of dulaglutide with insulin glargine, combined with prandial insulin lispro, in 884 patients with type 2 diabetes.	No cases of pancreatic cancer were identified.	[57]
MacConell et al./ Intention to treat populations from eight RCT	Safety profile of exenatide compared to liraglutide, sitagliptin, pioglitazone, metformin, and insulin glargine in 4,328 patients.	One case of pancreatic neoplasm with exenatide twice daily and three cases of prostate cancer with exenatide once weekly.	[41]
ESRD: dialysis-dependent end-stage renal disease			

Table 2: GLP-1 receptor agonists and cancer risk: summary of safety data obtained from randomized controlled trials (RCTs).

DPP-4 inhibitors and cancer risk

As for GLP-1 receptor agonists, numerous placebo-controlled and preclinical studies assessed the safety profile of DPP-4i [60-77]. In particular, a recent cohort study compared pancreatic cancer incidence between patients treated with DPP-4i vs. those treated with SU and TZD. Results showed that in both comparisons, no significant difference was observed; specifically, of 18,179 patients treated with DPP-4i and 63,746 with SU, only 26 patients in DPP-4i group and 177 in SU group have developed pancreatic cancer. For the other comparison, in 29,366 patients treated with DPP-4i and 26,332 with TZD, 52 vs. 54 presented pancreatic cancer, respectively. The risk of cancer associated with DPP-4i was lower compared to treatment with SU and similar to treatment with TZD [60]. Moreover, results of a

recent randomized, double-blind study, which have principally been evaluated in 14,671 patients the long term cardiovascular safety of sitagliptin vs placebo, showed that no significant differences were detected between-groups in rates of pancreatic cancer (p=0.32). Specifically, in sitagliptin and placebo groups 9 and 14 cases of pancreatic cancer were detected, respectively [61]. The safety of sitagliptin was also evaluated in a population of 3,201 patients with T2DM; as reported in the results, no cases of cancer were detected [62]. Finally, a recent parallel-arm, randomised, multicentre, double-blind study compared safety and efficacy profile of sitagliptin (25 mg) vs. vildagliptin (50 mg), the second marked DPP-4i, in 148 patients with T2DM and severe renal injury. Regarding safety results, no patient in both groups developed pancreatitis and no information was reported regarding the occurrence of cancer events [63]. Vildagliptin, added to insulin in a 24-week, multicenter, double-blind, placebo-controlled trial, showed a good safety profile. Results showed that no patients had cancer events [64]. Similarly, no malignant events were detected in EDGE study, in which efficacy and safety profile of vildagliptin was compared with oral antidiabetic agents (SU, TZD, glinides, α-glucosidase inhibitors, or metformin) in 45,868 patients with T2DM [65]. The evaluation of possible vildagliptin-induced pancreatic changes (predictive of pancreatitis and cancer in man) was conducted in two 104-week rodent carcinogenicity studies. Vildagliptin was administered at oral doses up to 900-1000 mg/kg (almost 200-240 times the maximum recommended dose in humans). Since no evidence of pancreatitis, pancreatic islet cell, acinar cell or ductal neoplasia were found, the authors concluded that vildagliptin seems to be safe and therefore no risk of cancer in humans has been associated with this drug [66].

The long-term safety of saxagliptin, the third oral DPP-4i marketed in European Union, was recently assessed vs. placebo, and in association to metformin, glyburide, or a TZD, in patients aged ≥ 65 years (n=205) and <65 years (n=1,055). According to the information reported by study authors, no cancer events have been reported [67]. SAVOR-TIMI 53 trial assessed the incidence of pancreatitis and pancreatic cancer in 16,492 type 2 diabetic patients who were randomized to receive saxagliptin (n=8,280) or placebo (n=8,212). Regarding to the occurrence of pancreatic cancer, data showed that this event occurred in 5 and 12 patients in the saxagliptin and placebo arms, respectively (p=0.09). Moreover, cancer events were detected in 327 patients treated with saxagliptin (3.9%) and in 362 patients who received placebo (4.4%) (p=0.15) [68]. Furthermore, results of a recent study, which compared the efficacy and safety of saxagliptin plus dapagliflozin vs. saxagliptin and placebo and dapagliflozin and placebo, showed that no events of bladder or breast neoplasms were observed [69]. Finally, a possible correlation between saxagliptin therapy and cancer was recently highlighted in a case report regarding a 66-years old male patient with metastatic carcinoid tumor who experienced a disease progression after initial treatment with saxagliptin. Authors suggested a possible association between the use of DPP-4 inhibitors and activity of carcinoid tumors [70].

The safety profile of linagliptin, as add-on to metformin and pioglitazone in patients with T2DM, was assessed in a multicentre, phase 3, randomized, double-blind, placebo-controlled study. Results revealed that no patients in each group reported pancreatic cancer, while only one patient in linagliptin group had colon cancer [71]. Similarly, no cases of pancreatic cancer were identified in 841 elderly patients with T2DM treated with linagliptin. Specifically, the incidence of cancer was higher in placebo group than linagliptin group (2.2% vs. 1.0%) [72]. Finally, supplementary safety data of linagliptin was obtained from 22 randomized, double-blind, Phase I-III, placebo-controlled studies, which enrolled a total of 7,400 patients (of which 4,810 received linagliptin and 2,590 placebo). Results showed that adverse events classified as neoplasms benign, malignant, and unspecified were observed with a frequency of 0.6% (number of events=29) in linagliptin group and 0.9% (number of events=24) in placebo group; no cases of pancreatic cancer were detected in both groups [73].

Alogliptin was the last DPP-4i marketed. One of the main studies which have evaluated its efficacy and safety profile was EXAMINE, a phase 3, multicenter, prospective, double-blind randomized trial in which alogliptin was compared with placebo on cardiovascular risk in 5,380 patients with T2DM and a recent acute coronary syndrome. As emerged from the results, there were no reports of pancreatic cancer, while there were 51 cases and 55 cases of not specified malignancy in placebo and alogliptin groups, respectively (p=0.77) [74,75]. In the same way, results from the study of Kaku et al. showed that patients treated with alogliptin and insulin, as well as those treated with placebo and insulin, did not experienced pancreatic cancer or other cancer events [76]. Finally, another multicentre, double-blind, active-controlled study evaluated the efficacy and safety (with particular attention to episodes of hypoglycaemia, major adverse cardiovascular events – MACE, and pancreatitis) of alogliptin (12.5 or 25 mg/day) vs. glipizide (5 mg) in combination with metformin in 2,639 type 2 diabetes patients. Study authors reported no case of cancer (Table 3) [77].

Authors/study characteristics	Assessment and population	Cases of cancer detected	Reference
Green et al./ event-driven RCT	Cardiovascular safety profile and cancer risk of sitagliptin compared to placebo in 14,671 patients.	Nine patients treated with sitagliptin and fourteen patients who received placebo had pancreatic cancer.	[61]
Kothny et al./ RCT	Efficacy and safety of vildagliptin compared with sitagliptin in 148 patients with type 2 diabetes and severe renal impairment.	No data were reported regarding to cancer events.	[63]
Ning et al./ RCT	Efficacy and safety of vildagliptin added on to insulin in 293 patients with type 2 diabetes mellitus.	No data were reported regarding to cancer events.	[64]
Scirica et al./ RCT	Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke in 16,492 patients who received saxagliptin (n=8,280) or placebo (n=8,212).	Five cases of pancreatic cancer in the saxagliptin group vs twelve in the placebo group.	[68]

		Cancer events were identified in 327 patients treated with saxagliptin and 362 patients who received placebo.	
Rosenstock et al./ RCT	Efficacy and safety of dual add-on of saxagliptin plus dapagliflozin vs. saxagliptin and placebo or dapagliflozin and placebo in 1,282 patients.	No cancer events reported.	[69]
Bajaj et al./ RCT	Safety profile of linagliptin vs. placebo, as add-on to metformin and pioglitazone, in 495 diabetic patients.	One patient in linagliptin group had colon cancer.	[71]
White et al./ RCT	Comparison of alogliptin vs. placebo on CV outcomes in 5,380 diabetic patients with a history of acute coronary syndrome.	No reports of pancreatic cancer. 51 cases and 55 cases of not specified malignancy were identified in placebo and alogliptin groups, respectively.	[74,75]
Kaku et al./ RCT	Efficacy and safety of alogliptin added to insulin in 280 Japanese diabetic patients.	No cases of pancreatic cancer or other cancer events.	[76]
Del Prato et al./ RCT	Efficacy and safety of alogliptin vs. glipizide in combination with metformin in 2,639 diabetic patients.	No cases of cancer were reported.	[77]
Iqbal et al./ Pooled adverse event data from 3 RCT	Long-term safety and tolerability of saxagliptin as add-on therapy to common antihyperglycemic drugs in 205 patients aged ≥ 65 years and 1,055 patients aged <65 years.	No data were reported regarding to cancer events.	[67]
Schernthaner et al./ Pooled analysis of 7 RCT	Safety and efficacy of linagliptin vs. placebo in 1331 diabetic patients.	No cases of pancreatic cancer were identified.	[72]
Lehrke et al./ Pooled Analysis of 22 RCT	Safety of linagliptin vs. placebo in 7,400 patients.	29 cases and 24 cases of neoplasms benign, malignant, and unspecified were observed in linagliptin and placebo groups, respectively. No cases of pancreatic cancer were detected in both groups.	[73]
Gokhale et al./ Observational study	Pancreatic cancer incidence among 18,179 patients initiating DPP-4 inhibitor treatment vs. those initiating SU and TZD.	No higher short-term pancreatic cancer risk with DPP-4 inhibitor treatment relative to SU or TZD treatment.	[60]
Ohmura et al./ Observational study	Efficacy and safety of sitagliptin in 3,201 Japanese diabetic patients.	No cases of cancer were detected.	[62]
Saab et al./ Observational study	Effectiveness and safety of vildagliptin as add-on to other OADs vs. other OAD combinations in 4,780 patients (2,513 received vildagliptin and 2,267 received other OADs).	No data were reported regarding to cancer events.	[65]
Clinical studies evaluating both GLP-1 receptor agonists and DPP-4 inhibitors.			
Leiter et al./ RCT	Safety profile of albiglutide compared to sitagliptin in 507 patients with type 2 diabetes and renal impairment.	One patient treated with albiglutide died for pleural mesothelioma. One patient treated with sitagliptin died for malignant melanoma. No cases of thyroid cancer were identified.	[53]
Weinstock et al./ RCT	Efficacy and safety of dulaglutide vs sitagliptin after 104 weeks of treatment in 1,098 patients.	Five cases of neoplasm in dulaglutide 1.5 mg group, three in dulaglutide 0.75 mg group, and five in sitagliptin group. One patient treated with sitagliptin died for uterine cancer, while one patient who received dulaglutide was diagnosed with papillary thyroid cancer.	[58]
Funch et al./ Observational study	Risk of pancreatitis and pancreatic cancer assessment in initiators of liraglutide, exenatide, metformin, pioglitazone or groups containing initiators of DPP-4 inhibitors or SU.	No increased risk for pancreatic cancer in association with liraglutide was identified.	[46]
SU: sulfonylureas TZD: thiazolidinediones			

OADs: oral antidiabetic drugs

Table 3: DPP-4 inhibitors and cancer risk: summary of safety data obtained from RCTs and observational studies.

Conclusion

As emerged by preclinical and clinical studies presented in this review, the risk of cancer associated to incretin-based therapies was very low. The 38 preclinical and clinical studies (20 for GLP-1 receptor agonists and 18 for DPP-4i) analysed have evaluated the safety profile of incretin-based therapies. In particular, safety results from clinical studies evaluating the tolerability of GLP-1 receptor agonists, showed that in a total of more than 13,000 patients with T2DM, 3 cases of pancreatic cancer, 3 cases of prostate cancers, 10 not specified neoplasms, 1 pleural mesothelioma and 1 case of thyroid cancer were diagnosed during the treatment with GLP-1 receptor agonists. Furthermore, results of a post-marketing safety assessment programme which used data from US commercial health insurance claims database showed that liraglutide had a lower incidence rate (IR/100,000 person-years) for pancreatic cancer compared to all the other therapies (19.9 vs. 33.0, respectively) [47]. Finally, as results of a carcinogenity study of dulaglutide emerged, the drug did not induce in transgenic mice C-cell hyperplasia or neoplasia [59].

Similarly to GLP-1 receptor agonists, even for DPP-4i on a total of more than 70,000 patients treated, 14 patients had pancreatic cancer, one patient had metastatic carcinoid tumor, one patient experienced colon cancer, thirty-four patients had not specified neoplasms, and one patient had malignant melanoma. Even if in EXAMINE and SAVOR-TIMI53 studies there were 382 cases of malignancies in patients treated with DPP-4i, this number was similar to number of cancer events occurred in patients in placebo groups. Furthermore, as emerged from a cohort study, the risk of cancer associated with DPP-4i was lower than SU and similar to TZD [60]. Also for these drugs, results from a recent pre-clinical study [66] have shown no evidence of pancreatitis, pancreatic islet cell, acinar cell or ductal neoplasia associated to vildagliptin. In one case report was found a possible correlation between saxagliptin therapy and progression of cancer in a 66-years old male patient [70].

Clearly, it is still not simple to define the correlation between these drugs and the cancer risk and, therefore, there is no definite evidence in favor or in contrast with this assumption. In conclusion, in the light of the data presented in this review, it is not possible to do certain deductions about the association incretin-based therapies and cancer risk especially because it is known that the same T2DM is a risk factor for cancer. For such reasons, it is important to improve post-marketing surveillance activities, such as the intensive monitoring of drug studies [78,79], which will increase the knowledge regarding this therapeutic class. Therefore, as T2DM is a chronic disorder and cancer events are rare, further long-term safety studies are needed.

Finally, very recently EMA and FDA have done a extensive evaluations of safety signals derived from post-marketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs. Moreover, FDA evaluated data from 250 toxicology studies, which included a total of 18,000 healthy animals, and EMA assessed clinical data regarding incretin-based therapies. At the end of this analysis, both agencies affirmed that the association incretin-based therapies/cancer is not supported by the current data.

For such reasons, it is very difficult to establish if the onset of cancer is due to the primary disease or the use of incretin-based therapies. However, according to EMA and FDA, it will be important to continue monitoring safety of patients treated with incretins [80].

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