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Drugs To Treat Type 2 Diabetes: Where Are We Going? And How To Face Their Risks

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Abstract

Glucagon like peptide 1 receptor (GLP1RA) agonists and Dipeptidyl peptidase 4 (DPP4i) inhibitors are drugs commonly used to treat type 2 diabetes. In some situation are the first choice drugs in treatment of this disease. It was demonstrated that glucagon like peptide (GLP1) has proliferative and anti-apoptotic effects on cells of biliary tree as the cholangiocytes [1,2]. Some of large randomised studies have shown the risks of these drugs in hepatobiliary cancers [1].

Keywords: Type 2 diabetes; Cholangiocarcinoma; GLP1 agonist receptor; DPP4 inhibitor

Abbreviations: GLP1RA: Glucagon Like Peptide 1 Receptor Agonists; DPP4I: Dipeptidyl Peptidase 4 Inhibitors; GLP: Glucagon Like Peptide; CPRD: Clinical Practice Research Data; WHO: World Health Organization; HF: Heart Failure; T2DM: Type 2 Diabetes Mellitus; SAVOR – TIMI 53: Saxaglipitin Assessment of Vascular Outcomes Recorded; TIMI 53: Trombolysis in Myocardial Infarction 53; MACE: Major Adverse Cardiovascular Events; TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; LDL: Low Density Lipoprotein

Introduction

The study published in the British Medical Journal , October 2018 by Azoulay et al. showed the risks of incretins based treatment and this rare and fatal cancer. They demonstrated this association in real world scenary. The DPP4i almost doubled cholangiocarcinoma risk. GLP1RA (liraglutide) also increased the risk without statistical significance [1]. The researches used Clinical Practice Research Data Link (CPRD), a primary care database that represents general UK population. The CPRD has documentation on demographic data, anthropometric data, laboratory results, code classification, diagnoses and procedures. This information is, therefore, of high quality and validity [3]. They defined the time patients used other drugs like insulin, acarbose, sulfonylurea, sodium-glucose-cotransporter-2 inhibitors and thiazolidinediones.

Metformin was defined as the drug of first choice. The exposure to these drugs were lagged by one year for latency purpose in order to reduce the risks of bias. The study added 154,162 subjects followed for a median of 4.6 to 11.2 years. They included the one year post cohort and entry in lag period. The median use of DPP4i and GLP1RA and other hypoglycemiants drugs was 1.9 to 10.1 years. Compared with the use of other second or third line drugs the DPP4i were associated with 77% increase in cholangiocarcinoma risk (hazard ratio 1.77, CI 95% 1.04-3.01). GLP1RA (liraglutide) was associated with a wide confidence interval (hazard ratio 1.97, CI 95% 0.83-4.66). There were seven adverse events with this drug [1].

The World Health Organization (WHO) Vigibase showed that compared to sulfonylureas and thiazolidinediones the use of DPP4i was associated with no increase of cholangiocarcinoma (OR 1.63, CI 95% 1.00-2.66). A similar increase in the reporting odds ratio was observed with use of GLP-1RA (OR 4.73, CI 95% 2.95-7.58). Conversely, the use of long acting insulin analogs was not associated with cholangiocarcinoma (OR 1.24, CI 95% 0.72-2.15) [1,4]. Increase of odds ratio was observed in a post hoc pharmacovigilance analysis for DPP4i and GLP-1RAs. In the Liraglutide Effect and Action

in Diabetes: Evaluation of Cardiovascular Outcome Results Trial (LEADER) with liraglutide was reported thirteen adverse events in comparison with eight adverse events in placebo group. A post hoc of this showed that all of these cancers were cholangiocarcinomas. The effect of both drugs on cholangiocytes are proliferative and anti-apoptotic associated to chronic inflamation of biliary epitelium, bile stasis and bacterial infection.

These complications happened mainly with GLP1RA and they were reported in LEADER trial (cholelitiases, cholecistites and cholangites). In the studies with DPP4 inhibitors were obseved that hazard ratio of cholangiocarcinoma incidence increased with cumulative duration roughly one to two years and more than two years. This data should be analysed with caution due to proved benefical effects in diabetes control although it is known that these drugs mainly DPP4 inhibitors of hepatic excretion might act among susceptible patients as tumors promoters. This study concluded that the use of GLP1RA and DPP4i increased cholangiocarcinoma risk [1,5]. The absolute risk is low and more studies are necessary to corroborate the results of Azoulay et al. [1].

And Now, How Are We Going To Proceed?

Are the benefits of these drugs greater than the risks?
The risks and benefits that are not related to biliary tree of DPP4i in other systems.

In Azoulay study there are several strenghts as the cohort only included use of naïve patients in terms of eliminated bias, because they did not include prevalent users. The researches compared incretins based treatment with second or third line drugs adjusting for indication use and describing the time of exposition of each drug [1].

Although there were some limitation in their study as the information of CRPD was given by general practitioners and not by specialists and the diagnosis of cholangiocarcinoma was not checked by specialists of CRPD. One study showed that there were more than 50% of non concordance of these gastrointestinal cancers between the CRPD and other datasets. Due to the rarity of these tumours not reported by CRPD specialists, a short drugs exposition (with a median time of 4.6 years), a large sample size (n=154.162) with few exposed events (27 events in DPP4i and 7 events in GLP1RA) and the impossibility of a secondary analysis among users of incretins based drugs [6,7].

So may consider, without fear, the benefits of these treatments in type 2 diabetes (T2DM). Regarding DPP4i cardiovascular benefits and diabetes control The DPP4i in Azoulay study were not separeted by the type of excretions (renal or hepatic) and we know that are diferences between them due to the risk of hospitalization to heart failure (HF) regardless the type of excretion [1]. Treatment with DPP4i improves the diabetes control for restoring the physiologic levels of GLP1. The half life of this incretin is short about 2-3 minutes and it is cleaved by the enzyme called DPP4. The activity of this enzyme is incresed in obese diabetics reducing the action of endogenous GLP1. The reduction in HbA1c is small (about 0.5-0.8%), mainly in post prandial blood glucose. The studies comprove this effect in post prandial blood glucose decreases cardiovascular (CV) mortality. These drugs do not cause hypoglycemia and weight reduction [8].

In the CARMELINA study a randomized cardiovascular trial, linaglipitina compared with placebo did not conferred neither CV benefits nor CV harms [8]. The SAVOR – TIMI 53 (Saxaglipitin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction 53) showed a significant relative risk (27%) of heart failure hospitalization. The three points MACE (Major Adverse Cardiovascular Events) as CV death known fatal myocardial infarction or known fatal ischemic stroke were similar to placebo [9]. Similar reports ocurred in EXAMINE study (Alogliptin after Acute Coronary Syndrome in Patients with type 2 Diabetes) the primary endpoints were no inferiority to placebo group but heart failure hospitalization (HF) relative risk increased 19%. Therefore the label of alogliptin and saxagliptin includes a warning for HF increased risk. These drugs should not be prescribed to patients with established heart and kidney diseases [8,10].

The TECOS study (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) did not show any increase in HF risk compared to placebo. Sitagliptin is now a second or third choice drug to primary cardiovascular disease (CVD), to patients with CVD established without HF or a fourth choice to established transiente ischemic attack or stroke. Renal adjustment is required for sitagliptin, saxagliptin and alogliptin, no dose adjustment is required for linagliptin [11].

The DPP4i are indicated by the American Association of Diabetes for patients without established artherosclerotic cardiovascular disease or chronic kidney disease or to treat T2DM patients with hypoglycemia predisposition or as a second choice drug with a lower cost if this is a major issue [7]. Regarding GLP1RA cardiovascular benefits and diabetes control. Liraglutide (the GLP1RA reported in Azoulay study) reduced blood glucose mainly post prandial glucose due to an increase in glucose dependent insulin secretion, glucagon secretion decrases and a delay in gastric emptying which leads to saciety and weight loss. GLP-1RA, liraglutide, is clinically available for the treatment of obesity at a higher dose (3.0 mg/d) [8].

The liraglutide dose needs to be titrate to reduce nausea

and vomiting. If the patient has pancreatitis history or if pancreatitis is suspected the treatment should be discontinued. There is not a need to dose adjustment in patients with renal or hepatic impairment although data in end-stage renal disease are limited. Care should be taken in patient with familiar history of thyroid medullary cancer even though this condition was just seen in animal studies. LEADER study with liraglutide was associated with a 20% reduction of new onset persistent macroalbuminuria, reduction in creatinine level increase, reduction in end-stage renal disease or death due to renal disease regardless of baseline estimated glomerular filtration rate. This study reported the three points MACE composite reduction by 13% (hazard ratio 0.87, CI 95% 0.78-0.97, p=0.01); all-cause mortality was reduced by 15% (hazard ratio 0.85, CI 95% 0.74-0.97, p=0.02). Liraglutide is the only GLP1RA approved by FDA to reduce the risk of MACEs in a adults with T2DM with established CVD [12].

There are a hypothetized mechanisms of GLP1RA to reduce CV events as blood pressure reduction. The consequence of this effect is a decrease in myocardial work, filling pressure and pre-/afterload in heart. Liraglutide diminishes systolic blood pressure by 1 to 6mmHg and reduces low density lipoprotein (LDL) cholesterol by up 16%. There are GLP1 receptors in the myocardium and vasculature but the role of these receptors in cardiovascular benefits are unknown [12,13]. We should take care prior initiating all T2DM therapies, specially with the new drugs as liraglutide and DPP4i, aimed to CVD risk reduction. A thoroughly discussion among clinician, patient and relatives is necessary and risks and benefits regarding tissues effects should be explained clearly, including drug cost, patient preference for oral or subcutaneous use, the need for weight reduction, hypoglicemics events control and risk of tumors incidence.

Conclusion

In conclusion, we need more trials in real world with these drugs!

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