Tirzepatide and Cancer Risk

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Abstract

Introduction: Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has revolutionized the management of type 2 diabetes and obesity. Due to its widespread use and chronic nature of treatment, assessing its long-term safety, particularly concerning cancer risk, is crucial. This descriptive review investigates existing research on the association between Tirzepatide use and cancer development.

Methodology: A review of published articles, including a meta-analysis of randomized controlled trials (RCTs), a retrospective analysis of the FDA Adverse Event Reporting System (FAERS) database, and peer-reviewed articles, was conducted, focusing on data from the last five years.

Results: Reviewed RCTs, primarily designed to evaluate efficacy, showed no significant increase in overall cancer events. Cases of pancreatitis were rare and evenly distributed between Tirzepatide and placebo groups in trials like SURMOUNT and SURPASS. Although some studies reported transient, reversible elevations in pancreatic enzymes, long-term follow-up studies specifically designed to assess pancreatic cancer risk are lacking, and the established link between chronic pancreatitis and pancreatic cancer necessitates caution. Regarding thyroid cancer, current evidence from RCTs and meta-analyses, along with FAERS data, does not conclusively link Tirzepatide to an increased risk.

In conclusion, while Tirzepatide demonstrates remarkable efficacy in weight loss and glycemic control, current research, primarily from short-to-medium-term clinical trials not specifically powered for cancer outcomes, shows no firm evidence of an increased cancer risk. Future RCTs with cancer risk as a primary outcome are essential to provide more definitive insights into the long-term safety profile of Tirzepatide.

Key words: Tirzepatide, cancer risk, pancreatic cancer, thyroid cancer

Introduction

Obesity is a pandemic and many anti-obesity medications have been formulated to target it, since it's a chronic condition; patients usually will need to have these medications for a long period of time and potentially be exposed to side effects. Assessing the safety of these medications is very important; the main aim of this descriptive review is focusing on Tirzepatide medication and its risk of cancer.

Tirzepatide is a revolutionized medication with dual-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor activation that has significantly changed the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. Tirzepatide achieved better glycemic control, body weight reduction in comparison with other anti-diabetic medication with acceptable side effects ,

Tirzepatide has been introduced and marketed as the most effective weight-loss medication of all times. Its sales from the Lilly group; Mounjaro and Zepbound brands were 3.11 billion USA dollars and 1.26 billion dollars respectively for Q3 of 2024 reflecting high demand and use of the medication . Prior to the introduction of these injectable medications, weight-loss surgery was the only effective way to achieve long standing weight loss, yet surgery was invasive and costly. The introduction of this class of medication has proven to be effective and satisfactory for patients.

Patients can get the medication by prescription or over the counter (self-referral/online pharmacies), making it readily available for use and difficult to track down reported side effects. In the Middle East and from my practice most patients get Tirzepatide over the counter and with minimal interaction with a pharmacist. This puts these patients at greater risk of side effects and potentially life-changing effects if they carry risk factors, for example the history of thyroid cancer or pancreatitis.

Tirzepatide shares side effects like those of other well established GLP-1 medications, including gastrointestinal symptoms, nausea, diarrhoea and vomiting, some of which are dose dependent. Other side effects include hypoglycemia, dizziness and abdominal pain to a lesser extent. Various other side effects were mentioned in literature, including pancreatitis risk .

Many studies have looked at various side effects and safety profile of Tirzepatide. Cancer risk was explored in a few research papers and within clinical trials, yet not separately or specifically trialed for that reason. These clinical trials were primarily aimed at proving efficacy and might not have fully unveiled safety issues. The aim of this descriptive review is to investigate research findings linking the use of Tirzepatide and its cancer risk.

Methods

Published articles looking at cancer risk associated with Tirzepatide were reviewed using online search engines; time frame was within the last 5 years and included review of a meta-analysis of randomized controlled trials (RCTs), a retrospective analysis of adverse events that utilized the FDA Adverse Event Reporting System (FAERS) database and some other peer reviewed articles as well as interesting case studies.

Tirzepatide and cancer risk

Theoretical risk of cancer was raised by studies linking use of GLP1 to thyroid and pancreatic cancer.

Tirzepatide (GLP1-GIP) Receptor analogues are contraindicated for use in any patient with personal or family history of thyroid cancer (medullary) as well as patients with multiple endocrine neoplasia type 2 (MEN2). This contraindication was as a result of animal studies . With this fact in mind, most studies and randomized trials excluded such patients.

The association between risk of chronic pancreatitis and pancreatic cancer is well established ; patients with a history of chronic pancreatitis were also excluded from large trials (like SCALE, STEP and SURMOUNT) making it difficult to assess risk of developing pancreatic change/ cancer in this specific population.

The link between obesity and increased risk of cancer is also well known, and patients who underwent weight loss surgery had a reduced incidence of obesity-associated cancers ' , so it could be argued that Tirzepatide as a weight loss agent potentially carries similar benefits and a reduced risk of cancer.

Results

A meta-analysis of randomized controlled trials (RCTs) evaluating the use of Tirzepatide in T2DM, setting a primary safety endpoint to be risk of any type of cancer and secondary end points of specific cancer types - up to April 24, 2024 , was reviewed and some interesting points were evaluated.

9 RCTs enrolling adults with T2DM and with obesity were included. Pediatric population/cancer patients – as well as patients with a family history of cancer were excluded; case studies and observational studies were also excluded from this meta-analysis.

SUPPASS trials were included in this meta-analysis - Seven RCTs have been published - five of which were global and two were regional in Japan.

SUPRASS 1 evaluated 3 doses of Tirzepatide (5-10 and 15mg) as monotherapy against placebo - while SURPASS 2 and 3 compared these 3 doses of Tirzepatide in efficacy and safety to injectable Semaglutide and Insulin Degludec respectively. SUPPASS 5 on the other hand checked the efficacy and safety of Tirzepatide to Insulin Glargine, compared to placebo.

Most of the adverse events were linked to gastrointestinal side-effects but for the purpose of this study we will focus on pancreatitis and cancer risk. SUPRASS trials (1-5) showed symptom free rise in pancreatic enzymes (amylase and lipase), that was reversible on discontinuation . No future studies followed up these patients to assess this risk or sequelae.

SURMOUNT-2 trial, showed three reported cases of pancreatitis, two were taking Tirzepatide 15mg and one on the placebo group. There were no cases of medullary thyroid or pancreatic cancer.

Previous SURMOUNT-1 showed similar results of four cases of pancreatitis, evenly distributed across the treatment and placebo groups. There was no reported medullary thyroid cancer. These results were consistent with previous SURPASS clinical trials.

Discussion

RCTs reviewed were of smaller numbers, and there were no reported cancer events, however researchers documented that their results should be handled with caution due to smaller numbers of trials, smaller numbers of participants and that the primary outcome of these trials were not predefined cancer outcome rather than as serious adverse event. It's very important to consider cancer as a risk and evaluated as a primary outcome in future studies. All studies reviewed considered cancer as a serious adverse event which could affect the true results reviewed.

Tirzepatide and Pancreatic cancer risk

Tirzepatide improves metabolic parameters and weight which positively affects patient's outcome and could have affected the risk of cancer. This statement should be considered with extra caution as studies have shown risk of pancreatitis with other GLP-1 (Exenatide, Liraglutide) and DPP-4 (Sitagliptin, vildagliptin etc.) use, chronic pancreatitis increased risk of pancreatic cancer by 26 fold in comparison with subjects not suffering from chronic pancreatitis, based on data of published studies .

Antidiabetic medications mentioned above are linked to episodes of acute pancreatitis which have a different etiology sequence to chronic pancreatitis, by which the latter have established links to histological changes including infiltration of T-cells and macrophages, fibrotic reaction and reduction in acinar cells, then the hallmark of developing cancer causing pancreatic intraepithelial neoplasia- intraductal papillary mucinous neoplasms and pancreatic duct glands. It takes years for this change to occur - 12 years for normal duct to change to tumor cell - then another 7 years to have metastatic capacity and another 3 years before the disease to be diagnosed and show clinical symptoms .

With these facts in place, any studies that don't cover at least 6 years of observation with any drug have a risk of missing or wrong interpretation on the risks of malignant disease. Such studies are yet to be initiated.

In a cohort historical study conducted in Israel follow up of 3,290,439 person-years of 543,595 adults with diabetes, 1,665 of them developed cancer of pancreas, yet there was no support of increased incidence of cancer over 7 years following starting GLP-1RA treatment to be found; as mentioned above monitoring above 7 years is required for more accurate results.

Subjects with a history of pancreatitis were excluded from large trials (SCALE, SURMOUNT and STEP). That is why it's still not clear what the actual risk of pancreatic cancer is in this population

Tirzepatide and Thyroid cancer risk

Pharmacological studies in rodents linked use of GLP-1RAs to development of medullary thyroid cancer, resulting in a warning on these agents against use in patients at risk. In human beings the expression of GLP-1 receptor in Thyroid C-cells is lower compared to rodents and treatment with Tirzepatide in RCTs has not been found to be associated with significant increase in calcitonin levels. Clinical studies from RCTs and meta-analysis suggest thyroid cancer to be a rare event, but without consistent evidence of increased risk in those receiving GLP-1RA, these studies concluded that there is no conclusive evidence of link between use of GLP1 RA and elevated thyroid cancer risk.

FDA adverse event reporting database published data on use of Tirzepatide and its safety profile in comparison with other GLP-1RA and it showed no increased risk in medullary thyroid cancer or pancreatobiliary side effects. In another study a comparison was made between Tirzepatide and Semaglutide and it showed that Tirzepatide has less association with side effects (pancreatitis, increased HBA1C and thyroid malignancy). When prescribing Tirzepatide, there is no information or guidance for routine thyroid ultrasound or calcitonin check, nonetheless patients with known thyroid nodules should be evaluated.

Tirzepatide and gastrointestinal cancer/ site specific cancer risk

A review of the literature involving a meta-analysis of 90 RCTs showed no significant effect on developing gastrointestinal cancer when GLP-1 was used in comparison with placebo. This was despite preclinical studies that suggested a possible link between GLP-1 use and tumorigenesis . This study was quite strong as the subjects were also followed for an average of just above three years, which is something that wasn't seen in other meta-analysis. Moreover, site specific analysis did not reveal any significant effect in increasing the risk of developing cancer. These studies also didn't confirm the protective effects reported in previous retrospective cohort studies regarding pancreatic, colorectal and hepatocellular cancer.

Conclusion

GLP-1 and in particular Tirzepatide have gained popularity recently due to their role in weight loss, and managing T2DM, Cardiovascular, hepatic and renal disease. Their effectiveness in achieving high weight loss threshold led to a thriving black market and significant concern over off-label use, which also led to shortages. Under these conditions, continuous monitoring and safety profile of these medications is paramount. Regarding the ongoing debate on the research world regarding whether GLP-1 based therapy can increase the risk for specific cancer like pancreatic, thyroid, gastrointestinal and other site-specific cancer, our conclusion from available research showed no firm evidence to favor this hypothesis nor evidence strong enough to rule out such an increased risk.

These clinical trials and research support the current guidelines recommending Tirzepatide for managing obesity and T2DM. This helps in counselling patients and reassuring them about their safety and that there is no association with an increased risk of cancer. Yet continued monitoring, as well as extended follow-up for existing RCTs/ New RCTs, using cancer risk as primary outcome is essential.

There are several outstanding questions regarding Tirzepatide protective mechanisms (anti-cancer pro-oncogenic) effects. Clinical trials addressing these questions will give us a clear idea about its use as anti-diabetic/weight loss as well as its safety in use in cancer patients.

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