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An Illustrated Review on Tazemetostat Drug on Diabetes Mellitus

Dr.Paspulpeti Kishore Kumar[1]*, Ramya Korani[1], Dr.V.V Rajesham[2], Dr.T. Rama Rao[3]

1. Department of Pharmacology, CMR College of Pharmacy, Kandlakoya(V), Medchal Road, Hyderabad, Telangana, 501401. India.

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ABSTRACT

Tazemetostat is an antineoplastic medication used to treat advanced epithelioid sarcoma, a rare slow-slow-growing form of tissue cancer, by preventing the formation of tumor or cancer cells. When a malignancy cannot be surgically removed or has metastasized to other regions of the body, tazemetostat is utilized. For specific epigenetic regulation, tazemetostat blocks the enhancer of Zeste Homolog 2 EHZ2. A rise in EHZ2 can result in gene mutations that induce sarcoma in individuals and can encourage the growth of cancer. the FDA's recent clearance of this oral medication. Additionally, Tazemetostat provides data from a case study that suggests GSK126 may facilitate the conversion of exocrine cells from a donor with type 1 diabetes mellitus (T1D) into beta cells, therefore partially restoring insulin activity. Researchers looked into the possibility of using small molecule inhibitors, namely GSK126, which target the EHZ2 methyltransferase protein, to promote beta cell regeneration in type 1 diabetes mellitus. Their findings were recently published in the Journal of Signal Transduction and Targeted Therapy.

Keywords: Tazemetostat, Epithelioid sarcoma,.EHZ2 methyltransferase, Type -1 diabetes mellitus

Introduction

Tazemetostat in treating cancer

The cancer medication tazemetostat functions as a strong selective enhancer of zest homolog 2 (EZH2) inhibitor. Tazemetostat inhibits the enhancer of zest homolog 2 (EHZ2) methyl transferase, potentially inhibiting the growth of cancer cells. Although it can develop in other parts of the body, the majority of instances of epithelioid sarcoma originate in the soft tissue beneath the skin of an extremity[5][6]. If the cancer is limited to a particular part of the body, surgery is thought to be the primary course of therapy. Other treatments include radiation or chemotherapy. Even with therapy, there is a significant chance that the illness may spread locally and regionally, and 50% of patients already have metastatic disease when they are first diagnosed. Since EHZ2 is a master regulator, any deregulation of this gene might encourage the growth of cancer. EHZ2 overexpression has been seen in a large number of solid cancers. This overexpression may encourage noticeably stronger gene suppression, which might increase immunity, metastasis, and cancer progression. Mutations affecting EHZ2 activity can arise in hematologic as well as solid cancers. Twenty percent of tumors have dysfunction in the sucrose nonfermentable chromatin remodeling complex[2]. A lack of function within the SNF complex components, such as the integrase interactors SMARCA4 and SMARCA2, might result in aberrant EHZ2 activation because sucrose nonfermentable can oppose the control of PRC2. Hematologic cancers may also have elevated EHZ2 activity. A somatic EHZ2 mutation that causes a gain-of-function and higher repression may be the cause of this enhanced activity[14]. These mutations are primarily seen in follicular lymphoma and diffuse large B cell lymphoma arising from germinal centers. This is because EHZ2 is highly expressed in pro-B and plays a significant role in the establishment of germinal centers. in addition to mutant EHZ2 in wild-type (WT) follicular lymphoma Additionally, EHZ2 can result in EHZ2 activity that can support the growth of cancer cells. Oncogenic alternations characterize follic lymphoma; oncogenesis interacts with wildtype EHZ2 to boost EHZ2 activity.[12][13].

Tazemetostat, also known as Tazverik, is a drug used to treat epithelioid sarcoma in adults and adolescents 16 years of age and older who have either locally advanced (cancer grown outside the organ it started in but has not yet spread to distant parts of the body) or metastatic (cancer cells spread to other parts of the body) epithelioid sarcoma that is not eligible for complete resection (surgically removing of all tissues, structure, or an organ). Tazemetostat is an oral, small molecule selective, S-adenosyl methionine competitive inhibitor of histone methyltransferase EHZ2 that may have anticancer properties, according to the NCI drug dictionary[3]. Tazemetostat suppresses the activity of both wild-type and mutant versions of EHZ2 preferentially when taken orally. The

methylation of histone H3lysine 27 (H3K27) is particularly prevented by inhibition of EHZ2[1]. EHZ2, a member of the methyltransferases (HMTs) class that is overexpressed or mutated in a variety of cancer cells and plays a critical role in tumor cell proliferation, is affected by this decrease in histone methylation, which changes gene expression patterns linked to cancer pathways and reduces tumor cell proliferation in EHZ2 mutated cancer cells. With manageable adverse effects such as weight loss, constipation, nausea, vomiting, etc.

History

Tazemetosat was authorized by the FDA in the United States in January 2020. This approval was based on the outcomes of a clinical trial (NCT02601950) that enrolled 62 individuals with metastatic or locally advanced epithelioid sarcoma. Tazemetostat 800 mg twice a day was administered to participants in the clinical trials until the illness worsened or the subject's level of toxicity was tolerable. Throughout the clinical studies, evaluations of tumor responses were carried out every eight weeks[4]. The trials assessed the proportion of patients whose tumors shrank completely or partially after therapy; the total response rate was 15%, with 1.6% of participants experiencing a full response and 13% experiencing a partial response. Six 67% of the nine participants that responded had a reaction that lasted six months or longer.

22 locations in France, the UK, Taiwan, Italy, Canada, Belgium, and the US participated in the experiment. Tazemetostat's application for expedited approval and orphan drug status was approved by the FDA. Epizyme received FDA clearance for Tazverik.

Relation Ship Between The Anticancer Drug In Producing Beta Cells In Type 1 Diabetes Mellitus Showing Antidiabetic Activity.

Since beta cells in the pancreas create, store, and release insulin, their elimination by the host's immune system causes dysregulation of blood glucose levels. Type 1 diabetes mellitus is a chronic disorder that affects 4000 million people worldwide. While medication can be used to control blood sugar, more modern pharmacological therapies address the clinically effective loss of beta cell mass by transplantation.

The science is divided on the existence of pancreatic ductal progenitors for the development of beta cells due to inconsistent findings from observational studies, models of pancreatic damage, and other relevant models. Furthermore, data from case studies indicates that GSK126, an FDA-approved EHZ2 inhibitor, may be able to partially restore insulin function by facilitating the type 1 diabetes mellitus donor's exocrine cells to develop into beta-like cells. Extending these conclusions, the current study's researchers described GSK126 and Taz's capacity to reinstate crucial beta-cell functions, such as isolated exocrine function.[7,8].

Background

Activating Zeste Homolog's Enhancer Two switch/sucrose non fermentable (SWI/SNF) complex abnormalities or EHZ2 mutations can cause aberrant histone methylation, oncogenic transformation, and a proliferative reliance on EHZ2 activity. We sought to examine the pharmacokinetics, pharmacodynamics, safety, and clinical efficacy of tazemetostat, a first-in-class selective EHZ2 inhibitor, in this first-in-human research. In patients with advanced solid tumors, such as epithelioid sarcoma, and refractory beta-cell non-Hodgkin lymphoma, hemostat had a good safety profile and antitumor efficacy. Phase 2 trials in adults and a phase 1 study in children are now recruiting patients with beta cells non-Hodgkin lymphoma and INI1-negative or SMARCA4-negative malignancies in order to conduct more clinical research into tazemetostat monotherapy.

Australian researchers have explored the use of small molecule inhibitors, especially GSK126 EHZ2 methyltransferase protein, to drive beta-cell regeneration in type 1 diabetes mellitus. Their findings were published in the journal signal transduction and targeted therapeutics. They discovered that beta-cell regeneration appears to be positively impacted by stimulation with EHZ2 inhibitors, which may open up new possibilities for the development of T1D treatments[8].

About the study

The structural consequences of GSK126 and Taz binding to EHZ2 methyltransferase were examined by the application of molecular modeling. Three brain-dead donors with different age ranges and diabetes statuses were used to obtain ex vivo exocrine tissues (islet, acinar, and ductal): a young T1D donor, an adult T1D donor, and a healthy adult without diabetes. After that, the tissue was stimulated for 48 hours with either 1mu Taz or 10mu GSK126. Using quantitative reverse transcription polymerase chain reaction and ribonucleic acid (RNA) sequencing, transcriptome profiling of the tissues was carried out. Additionally, immunofluorescence labeling and chromatin immunoprecipitation tests were carried out. In addition, the scientists created the glucose-stimulated insulin secretion (GSIS) test to assess the ability of diabetic exocrine cells to regenerate in both hyperglycemic and basal insulin environments.[9].

Scientists in Australia discovered that Taz had a higher binding affinity than GSK126 in the EHZ2 catalytic domain in their modeling tests. GSK126 and Taz may have an impact on the expression of genes related to glucose metabolism and exocrine hormone control, in addition to endocrine indicators, according to transcriptome profiling and PCR investigations.[14] Refractory H3K27me3 concentration of endocrine genes was seen to decrease in exocrine tissues after EHZ2 inhibition. In current research. Insulin production was demonstrated by EHZ2-inhibited ductal cells positive for cytokeratin-19 using immunofluorescence labeling. Furthermore, insulin could be secreted by activated exocrine cells in a glucose-responsive manner, suggesting that mature beta-cell activity and glucose homeostasis were functioning in exocrine tissues.

H3K27me 3 concentration was reduced in human pancreatic ductal epithelial cells treated with EHZ2 inhibitors, GSK126 and Taz. Even after going back to drug-free circumstances after 96 hours, there was a little persistence of the transcriptional alterations. The number of CK19/INS-positive cells in these cells was not substantially changed by EHZ2 inhibitor stimulation. When drugs were stimulated, insulin secretion increased. It then decreased when the drugs were removed, but it remained greater than the control under glucose stimulation, indicating a long-lasting effect on insulin secretion[9].

Review findings

Building on the work of other researchers, this study demonstrates the anticancer and antidiabetic effects of EHZ2 inhibitors as well as the epigenetics-mediated method of transforming terminally differentiated exocrine cells into beta-cells that produce insulin. For the first time, it demonstrates how Taz affects the expression of insulin in exocrine ductal cells taken from a pancreas that has diabetes. The work is just the second case study in which progenitor capacity was restored in a kid with T1D, which limits its applicability. Furthermore, not all ductal cells will undergo beta-cell transformation, and better methods or surgical excision of pancreatic ductal cell resection may increase conversion efficiency.

The article on how EHZ2 inhibitors promote beta-cell regeneration in young and adult type diabetes donors from article number (2024) was published in the most recent issue of Signal Transduction and Targeted Therapy on January 1, 2024. It described a case study in which insulin gene expression from pancreatic ductal cells was partially restored by converting the refractory nature of chromatin using GSK126, an FDA-approved EHZ2 inhibitor. Three donors' pancreatic tissues were resected, and small chemical inhibitors, GSK126 and Tazemetostat, were obtained to study the reactivation of pancreatic progenitor cells for regenerative beta-cell potential. Studies using predictive molecular modeling were conducted to examine the effects of structure on binding to the catalytic domains of the EHZ2 protein.

The findings indicate that EHZ2 is bound by small molecule inhibitors, with Taz exhibiting a greater binding affinity at the catalytic domain. Energy contributions from chromosomes Y661 and C663 in the catalytic SET domain and I109 and Y111 in the protein region SAL of EHZ2 are shown by molecular dynamics simulations. Chromosomes C663, F665, and F686, which contain residues that significantly aid in the binding of the SET domain, are also implicated in the binding of the SAH/SAM cofactor, which is suggestive of competitive binding by GSK126 and TAZ.[10][11].

Conclusion

In summary, tazemetostat is a new EHZ2 inhibitor that has demonstrated efficacy and safety in clinical studies, along with manageable side effects. That being said, tazemetostat is only the start of targeted epigenetic regulators. EHZ2 is implicated in lymphomas and several other solid tumors' oncological processes. The results of the study and the anticancer effect of tazemetostat suggest that default suppression may be connected to the possibility of restoring pancreatic ductal cells' capacity to produce regenerating beta cells. In T1D, targeting refractory chromatin by blocking EZH2-dependent silencing may aid in overcoming regeneration obstacles and regaining the activity of insulin-producing beta-cells. The results provide new hope for therapeutic intervention for T1D patients while also indicating the need for more study.

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