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Cancer risks of anti-hyperglycemic drugs for type 2 diabetes treatment – a clinical appraisal

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ABSTRACT

Aim: A clinical appraisal of existing scientific literature sought to assess the need for long-term prospective epidemiological studies to investigate an increased cancer risk of anti-hyperglycemic medication in type 2 diabetes.
Method: A focus statement was formulated as: "With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks." Field surveys were sent to practicing physicians and endocrinologists to identify the currently prevalent level of acceptance of this statement. Subsequently, a meeting with a six-member panel of key opinion leaders was held to discuss published evidence in support and against the statement. This publication reviews the publications and discussion points brought forth in this meeting and their effect on statement acceptance by the panel.
Results: Whereas the majority of field survey responders primarily agreed with the statement, panel members were divided in their statement support. This division remained intact after review of the literature.
Conclusions: While there was evidence that type 2 diabetes is associated with an increased risk of cancer, existing studies seemed insufficient to definitively demonstrate a link between cancer risk and use of specific anti-hyperglycemic therapies.

1. Introduction

According to the Centers for Disease Control and Prevention (CDC), approximately 29 million people in the US have diabetes mellitus, and 90%–95% of the cases comprised type 2 diabetes mellitus (T2DM) [1]. T2DM can lead to blindness, renal failure, cardiovascular disease, amputation of extremities, and premature death. In the last decades, many new therapies have become available for treating T2DM. The main T2DM drug classes include agents that either stimulate insulin secretion/improve beta cell function (sulfonylureas, DPP4 inhibitors, GLP1 receptor agonists), reduce hepatic glucose production (biguanides), delay digestion of carbohydrates (alpha-glucosidase inhibitors), improve insulin action (thiazolidinediones), or decrease glucose reabsorption by the kidney (SGLT2 inhibitors) [2]. Because some of these drugs have been in use for only a short time, concerns of potential long-term adverse effects have not been addressed by a large body of research as yet.

Evidence suggests that diabetes may be associated with an increased risk of cancer [3,4]. The mechanisms are yet to be fully understood, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis [5]. The treatments that cause hyperinsulinemia, such as sulfonylurea and exogenous insulin, have been suggested to increase cancer risk [6–9], while treatments that decrease insulin resistance, such as metformin, may reduce the risk of cancer development [10–14].

Notwithstanding these suggested links, clinical studies have generated conflicting data on the effects of these and other specific anti-hyperglycemic drugs on cancer risk. A clinical appraisal meeting was therefore held in December 2014 to investigate the current status and perceptions. A focus statement was formulated and members of a

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six-person panel of experts were then asked to present an extensive literature review either in support of or in opposition to the statement. Here, we discuss the contents, flaws, and effects of the various studies brought forth in the appraisal meeting to validate or refute a statement related to the link between T2DM medications and cancer risk, and the effect of the panel discussions and presentations on panel members' opinions.

2. Appraisal design

To critically examine the perceptions of practicing physicians in the field regarding statements relevant to T2DM treatments, an online survey was sent out to 40,000 primary care physicians, family practitioners, internal medicine specialists, and endocrinologists, 1.1% of which responded. After elimination of doctors without T2DM treatment experience, responses from 402 physicians (210 primary care physicians, family practitioners or internal medicine specialists, and 192 endocrinologists) were summarized. The physicians were asked to grade their level of support regarding the following statement: "With a higher risk of cancers in patients with type 2 diabetes, all anti-hyperglycemic drugs should undergo long-term, prospective epidemiological studies for cancer risks." Support levels are shown in Table 1 and were defined to be on a scale of 1 to 6, with 1 representing complete support and 6 representing complete rejection.

Subsequently, an expert panel of six subject-matter experts gathered in December 2014 to discuss the statement. With the focus on safety, the goal of that meeting was to create an unbiased, critical, systematic scientific review of existing data, guidelines, and practices. One panel member was selected to present the current literature in support of the statement, and another panel member was tasked with presentation of the literature in opposition of the statement. In these panel presentations, particular attention was paid to study design, methodologies, and numbers and types of patients involved. Following the presentation of evidence for each statement, the panel evaluated the overall nature of evidence that was presented, which included the following categories: (1) Evidence obtained from meta-analysis, including at least one large, randomized controlled trial (RCT); (2) Evidence obtained from either meta-analysis, including at least one small RCT, or from at least one well-designed, large RCT; (3) Evidence obtained from well-designed cohort or case-controlled studies; (4) Evidence obtained from case series, case reports, or flawed clinical trials; (5) Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees; (6) Insufficient evidence to form an opinion.

The panel members were also asked to indicate their degree of acceptance of the statements before and after the presentation, using the level definitions presented in Table 1.

3. Literature review

3.1. Rationale and definition of statement

The statement was developed to challenge the notion that long-term, prospective epidemiological studies are necessary to evaluate the cancer risks of every hyperglycemic drug involved in T2DM treatment regimens. Although it does appear that T2DM is associated with an increased cancer risk, it remains unclear whether: (i) the association is largely due to shared risk factors; (ii) diabetes itself alters cancer risk; (iii) the risk of cancer development is modified with medications administered to combat T2DM; or (iv) a combination of all three of these assumptions applies.

In the past, public awareness had been raised to the possibility of cancer risks associated with certain treatments such as insulin glargine. Evidence from observational studies suggested that, in addition to glargine, other glucose-lowering oral agents are also associated with either an increased or reduced risk of cancer [6–14]. However, these studies were unable to reliably determine whether the observed associations were real (ie, whether glucose-lowering medications had a direct harmful or beneficial effect on cancer risk) and/or due to confounding factors.

In light of this, the statement was developed to investigate whether a general need for long-term prospective epidemiological evaluation of possible carcinogenic properties of any hyperglycemic drug exists. An in-depth examination of existing scientific literature was performed to provide guidance and help determine whether there is a direct link between cancer risk and use of specific anti-hyperglycemic therapies.

3.2. Literature search criteria

Literature in support of the statement was identified through a PubMed search in October 2014 using the keywords "anti-diabetic drugs," "cancer," "risks," and "diabetes." Studies published from 2010 onwards involving human subjects were considered. From the 845 titles, 252 abstracts were selected for further review. Of these, 40 abstracts were found to be most relevant to the research question. The panelist then selected twelve publications for presentation in the meeting.

Literature refuting the statement was also retrieved through a PubMed search in October 2014 using the key phrases "type 2 diabetes mellitus," "anti-hyperglycemic therapy," "cancer," and "neoplasms." Additional keywords included "glucose-lowering drugs," "hypoglycemic agents," and "anti-diabetic drugs." Results were limited to human studies with a publication date of 2008 or later. From the 603 titles, 196 abstracts were selected for further review. Of these, 53 abstracts were found to be most relevant to the research question. The panelist finally selected 22 publications to be presented at the meeting.

3.3. Literature in support of the statement

The first papers presented in support of the statement established the existence of an increased cancer risk for T2DM patients. According to a review authored by Andersen [3], epidemiologic evidence strongly suggests that people with diabetes are at significantly higher risk for several forms of cancer, in particular pancreatic ductal adenocarcinoma. Cannata et al. [15], sought to establish the reason, and postulated that in T2DM, insulin resistance results in elevated insulin levels, which may lead to cancer through direct effects on cancer cells via the insulin receptor (IR) and the insulin-like growth factor I receptor (IGF-IR).

The following paragraphs discuss the presented literature that investigated cancer risks for specific drug types.

3.3.1. Insulin and insulin analogs

A meta-analysis of observational studies assessed the risk of cancer during insulin treatment [16], and summarized that six out of ten cohort studies and one out of five case-control studies found a statistically significant positive association between insulin treatment and cancer.

The only RCT to address this issue, ORIGIN (Outcome Reduction with Initial Glargine Intervention), was an international, long-term RCT comparing insulin glargine with standard care in a 2 × 2 factorial design that included n-3 fatty acids and placebo in 12,537 T2DM

Table 1
Definition of levels of support for statements.

Support level	Definition
1	Agree completely
2	Agree with minor reservations
3	Agree with major reservations
4	Reject with minor reservations
5	Reject with major reservations
6	Reject completely

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