In Reply: Telotristat Ethyl for Patients With Carcinoid Syndrome Associated With Chest Pain and Hypertension

To the Editor:

In the January 2018 issue, Dr Kasi recently reported prescribing telotristat ethyl to 3 patients with carcinoid syndrome and observing grade 3 chest pain and hypertension in all of them, each case within 1 month of initiating treatment. Here we review the clinical trial experience and postmarketing surveillance for these adverse events.

The safety and efficacy of telotristat ethyl were established during phase 3, randomized, placebo-controlled, double-blind clinical trials enrolling subjects with carcinoid syndrome not adequately controlled by current somatostatin analog therapy.

During the TELESTAR study, subjects received double-blind placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg 3 times daily for 12 weeks (N = 135). Subsequently, they entered a 36-week open-label extension phase during which subjects received telotristat ethyl 500 mg 3 times daily (N = 115). During the TELECAST study, subjects received double-blind placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg 3 times daily for 12 weeks (N = 76).

In the integrated safety analysis data from the TELESTAR and TELECAST studies, the incidences of chest pain during the 12-week double-blind treatment period among subjects treated with placebo and telotristat ethyl were 0 and 0.7% (n = 1), respectively. The incidences of hypertension among subjects treated with placebo and telotristat ethyl were 1.4% (n = 1) and 2.9% (n = 4), respectively. In addition, 1 placebo patient and no patient on telotristat ethyl experienced increased blood pressure. At the end of the double-blind treatment period, the mean change from baseline in systolic blood pressure among all subjects who initiated telotristat ethyl was +1 mm Hg. Similarly, the mean change in diastolic blood pressure was +1 mm Hg. There were no serious adverse events related to chest pain or hypertension in these phase 3 studies.

Among subjects with preexisting carcinoid heart disease treated with telotristat ethyl, there was no difference between the adverse event profile of this subgroup and the overall study populations.

During the postmarketing experience with telotristat ethyl through December 1, 2017, Lexicon Pharmaceuticals has received a small number of reports for chest pain and hypertension, which is consistent with the clinical trial experience. Postmarketing safety surveillance efforts are ongoing.

All authors are Lexicon Pharmaceuticals, Inc; employees.

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Wenjun Jiang, MD
Raul Perez-Olle, MD, PhD
Pablo Lapuerta, MD
Lexicon Pharmaceuticals, Inc
Basking Ridge, NJ
PLapuerta@lexpharma.com

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Metformin and Pancreatic Cancer Risk in Patients With Type 2 Diabetes

To the Editor:

Patients with pancreatic cancer (PC) have very poor prognosis, and the 5-year survival is as low as 6%.1,2 Risk factors of PC include diabetes, obesity, smoking, pancreatitis, and family history.3 Although metformin use in diabetes patients is associated with a reduced risk of PC in a meta-analysis,4 a recent case-control study conducted in the United States did not confirm such a protective effect.5 Because data from Asian populations are still sparse, this study evaluated whether metformin might reduce PC risk in Taiwanese patients with type 2 diabetes mellitus, using the reimbursement database of Taiwan’s National Health Insurance.

Detailed methodology has been reported previously.6,7 Disease diagnoses were based on the International Classification of Diseases, Ninth Revision, Clinical Modification. Diabetes was coded 250.XX and PC was coded 157.

A cohort of 12,616 pairs of metformin ever users and never users matched on propensity score using the Greedy 8 → 1 digit match algorithm was enrolled from new-onset diabetes patients diagnosed during the period from 1999 to 2005, following the steps shown in Figure 1. Patients with a diagnosis of pancreatic disease (International Classification of Diseases, Ninth Revision, Clinical Modification 577), alcohol-related diagnoses (291, 303, 535.3, 571.0–571.3, and 980.0), and gallstone (574.00, 574.01, 574.10, 574.11, 574.20, 574.21, and A348) were excluded to avoid their residual confounding.

Propensity score was derived from the date of entry plus covariates including age, sex, occupation, living region, hypertension (401–405), dyslipidemia (272.0–272.4), obesity (278), nephropathy (580–589), eye disease (250.5, 362.0, 369, 366.41, and 365.44), stroke (430–438), ischemic heart disease (410–414), peripheral arterial disease (405.0, 785.4, 443.81, and 440–444), chronic obstructive pulmonary disease (490–496), tobacco abuse (305.1, 649.0, and 989.84), history of Helicobacter pylori infection, insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone, pioglitazone, angiotensin converting enzyme inhibitor/angiotensin inhibitor/antihypertensive therapies, and antiplatelet agents.

All patients with new PC diagnosis were included (N = 4,338). The match ratio was 1:1. The matched pairs were compared using the log-rank test, and the hazard ratios (HR) of PC were calculated in multivariable Cox regression models. The incidence of PC among metformin users was 0.61% per 100 patient-years and among never users was 1.01% per 100 patient-years. The adjusted HR for development of PC was 0.59 (95% confidence interval, 0.37–0.94).

This study suggests that metformin may reduce the risk of PC in type 2 diabetes patients receiving metformin therapy. Further studies are needed to confirm these findings.

Raul Perez-Olle, MD, PhD
Pablo Lapuerta, MD
Lexicon Pharmaceuticals, Inc
Basking Ridge, NJ
PLapuerta@lexpharma.com

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New-onset type 2 diabetes patients diagnosed during 1999-2005 and had been followed in the outpatient clinics with prescription of antidiabetic drugs for 2 or more times

N = 423,949

- Excluding patients with type 1 diabetes mellitus (n = 2400)
- Excluding patients with missing data (n = 746)
- Excluding patients who had been diagnosed (at outpatient clinics or hospitalization) of any cancer before entry or within one year of diabetes diagnosis (n = 45,886)
- Excluding patients with pancreatic disease (n = 18,388)
- Excluding patients with alcohol-related diagnoses (n = 19,501)
- Excluding patients with galbladder (n = 40,743)
- Excluding patients aged <25 years (n = 14,943) at entry
- Excluding patients aged >75 years (n = 33,148) at entry
- Excluding patients who had been followed up for <180 days (n = 6275)

Unmatched cohort of ever and never users of metformin

| Metformin ever users | N = 229,303 (94.8%) (Pancreatic cancer = 317 (0.14%)) |
|----------------------|------------------------------------------------------|
| 1:1 matched pairs of ever and never users of metformin |
| Metformin ever users | N = 12,616 (Pancreatic cancer = 13 (0.10%)) |
| Metformin never users | N = 12,616 (Pancreatic cancer = 25 (0.20%)) |

FIGURE 1. Flowchart showing the procedures in selecting the matched pairs of ever and never users of metformin.

TABLE 1. Incidence Rates of and Hazard Ratios for Pancreatic Cancer by Metformin Exposure

| Metformin | Incident Case Number | Cases Followed | Person-Years | Incidence Rate (Per 100,000 Person-Years) | Hazard Ratio (95% Confidence Interval) | P |
|-----------|----------------------|---------------|--------------|------------------------------------------|-------------------------------------|---|
| Never users | 25 | 12,616 | 57,358.1 | 43.59 | 1.000 |
| Ever users | 13 | 12,616 | 60,199.8 | 21.59 | 0.492 (0.252–0.961) | 0.0379 |
| Tertiles of cumulative duration of metformin therapy, mo |
| Never users | 25 | 12,616 | 57,358.1 | 43.59 | 1.000 |
| <21.80 | 6 | 4160 | 14,966.6 | 40.09 | 0.900 (0.368–2.198) | 0.8168 |
| 21.80–47.07 | 6 | 4168 | 20,818.0 | 28.82 | 0.648 (0.266–1.581) | 0.3406 |
| >47.07 | 1 | 4288 | 24,415.2 | 4.10 | 0.094 (0.013–0.692) | 0.0203 |

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receptor blocker, calcium channel blocker, statin, fibrate, and aspirin. Standardized difference was calculated for each covariate, and a cutoff greater than 10% may indicate potential confounding.6,7 The incidence density of PC was calculated for different subgroups of metformin exposure. Follow-up started on the first day of the use of antidiabetic drugs and ended on December 31, 2011, at the time of a new diagnosis of PC, or on the date of the last reimbursement record. Hazard ratios were estimated by Cox proportional hazard model incorporated with the inverse probability of treatment weighting using propensity score.6,7 Results showed that metformin ever users and never users were well matched with none of the covariates having a standardized difference of greater than 10% (data not shown). The incidence of PC and hazard ratios by metformin exposure are shown in Table 1. The findings supported that metformin use was associated with a significantly lower risk of PC, especially when it had been used for approximately 4 years.

Molecular pathways related to the beneficial effects of metformin on PC development have been recently reviewed.2 These may include activating the liver kinase B1 and adenosine monophosphate-activated protein kinase, lowering circulating insulin, promoting apoptosis and autophagy, inhibiting cell division, and activating the immune system. Metformin
may also suppress PC cell growth through inhibiting inflammatory signaling or downregulating the expression of proto-oncogenes. Pancreatic cancer cells overexpress enzymes involved in fatty acid and cholesterol synthesis, and metformin may affect de novo fatty acid synthesis via down-regulation of specificity protein transcription factors.

This study avoided selection bias by using a nationwide database covering more than 99% of the Taiwan’s population. Potential bias related to self-reporting was much reduced by using medical records. Detection bias due to different socioeconomic status was less likely in the present study because the drug cost-sharing is low in the National Health Insurance health care system and can always be waived in patients with low income, in veterans, and in those who received prescription refills for chronic diseases.

Prevalent user bias, indication bias, and immortal time bias are major methodological limitations in pharmacoepidemiological studies, but these have been carefully addressed as discussed previously. There are some limitations. First, the present study could not completely consider the effect of some important risk factors. For example, 5% to 10% of the cases may have familial aggregation, but we did not have information of family history or genetic markers for analyses. Second, because of the lack of actual measurement data of some confounders such as anthropometric factors, smoking, alcohol drinking, lifestyle, nutritional status, fat consumption, and fiber intake, it is also not possible to exclude their residual impacts.

In summary, this study supports a lower risk of PC associated with metformin use in Taiwanese patients with type 2 diabetes mellitus, especially when it has been used for more than 4 years. The potential usefulness of metformin on the prevention of PC in either the diabetes patients or in nondiabetes individuals is worthy of more extensive study.

The author declares no conflict of interest.

Chin-Hsiao Tseng, MD, PhD
Department of Internal Medicine
National Taiwan University College of Medicine
Taipei, Taiwan
ccks@ms6.hinet.net

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Patients With Pancreatic Ductal Adenocarcinoma Have High Serum Galactin-9 Levels
A Sweet Molecule to Keep an Eye On

To the Editor:

Prognosis for pancreatic adenocarcinoma (PADC) tends to be poor because of its delayed diagnosis and aggressive behavior. Whereas some solid tumors such as breast cancer have survival rates of 90%, PADC has rising rates of mortality and a 5-year survival rate approximately 9%. Therefore, diagnosing PADC early is the most important factor of improving its prognosis. As part of the lectin family, galectins perform their primary biological functions by interacting with β-galactosides carbohydrate structures in proteins, peptides, and lipids. Galactin-9 (Gal-9) is a tandem-repeat type galectin with two carbohydrate-recognition domains. Studies have revealed that Gal-9 modulates various biological functions, including tumor cell apoptosis, aggregation, and adhesion, and participates in the progression of different tumors. By extension, altered galectin expression has diagnostic or prognostic value in different types of cancer, including gastric and colon cancers.

In this article, we present an evaluation of Gal-9 expression in the serum and tissue of patients diagnosed with PADC.

MATERIALS AND METHODS

After the approval of the ethics committee, blood samples were collected from 34 patients with confirmed diagnoses of PDAC. Galectin-9 serum levels were quantified by enzyme-linked immunosorbent assay sandwich following the supplier’s instructions (R & D Systems, Minneapolis, Minn). None of the patients had received any anticancer therapy before sample collection. Formalin-fixed paraffin-embedded PADC specimens were also retrieved from the archives of the Department of Pathology at the Hospital of Cancer in Pernambuco, Brazil.

Tissue Gal-9 expression was evaluated by immunohistochemistry. Deparaffinized sections were incubated with primary antibody (rabbit polyclonal) anti-Gal-9 (1:50) for 2 hours. Gastric tissue was used as a positive control, and in the negative control, the primary antibody was replaced with nonspecific IgG in a PBS-BSA 1% solution. Each section image was captured using an Eclipse TS2 microscope (Nikon, Melville, NY).

RESULTS

Patients with PADC (n = 34) and healthy controls (n = 66) were paired by sex (P = 0.11130) and age (P = 0.1205). Females represented 71% of the PADC group and 81% of control group. The median age of the control group and PADC group were 62 and 64 years, respectively. All 34 serum samples from patients with PADC were Gal-9 positive and present a significantly higher level (median, 46.88 [interquartile range, 4457–8647] pg/mL) than that of controls (median, 46.88 [interquartile range, 46.88–46.88] pg/mL), as shown in Figure 1 (left panel). To investigate possible sources of Gal-9 production, we performed an immunostaining reaction using formalin-fixed paraffin-embedded samples of PADC. Histologically, Gal-9 staining was positive in all cases analyzed except one. Neoplastic cells presented homogeneous cytoplasmic staining.