[Original Research]

CHEST

The Risk of TB in Patients With Type 2 Diabetes Initiating Metformin vs Sulfonylurea Treatment

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BACKGROUND: Metformin and the sulfonylureas are common initial antidiabetic agents; the former has demonstrated anti-TB action in in vitro and animal studies. The comparative effect of metformin vs the sulfonylureas on TB risk in patients with type 2 diabetes mellitus (T2DM) remains unclear.

METHODS: In this retrospective cohort study, patients without chronic kidney disease who received a T2DM diagnosis during 2003 to 2013 were identified from the Taiwan National Health Insurance Research Database. Participants with ≥ 2 years of follow-up were reviewed and observed for TB until December 2013. Patients receiving metformin ≥ 60 cumulative defined daily dose (cDDD) and sulfonylureas < 15 cDDD in the initial 2 years were defined as metformin majors; it was the inverse for sulfonylurea majors. The two groups were matched 1:1 by propensity score and compared for TB risk by multivariate Cox regression analysis.

RESULTS: Among 40,179 patients with T2DM, 263 acquired TB (0.65%) over a mean follow-up of 6.1 years. In multivariate analysis, the initial 2-year dosage of metformin, but not that of the sulfonylureas, was an independent predictor of TB (60-cDDD increase (adjusted hazard ratio [HR], 0.931; 95% CI, 0.877-0.990) after adjustment by cofactors, including adapted diabetes complication severity index. Metformin majors had a significantly lower TB risk than that of sulfonylurea majors before and after matching (HR, 0.477; 95% CI, 0.268-0.850 and HR, 0.337; 95% CI, 0.169-0.673; matched pairs, n = 3,161). Compared with the reference group (initial 2-year metformin < 60 cDDD), metformin treatment showed a dose-dependent association with TB risk (60-219 cDDD; HR, 0.860; 95% CI, 0.637-1.161; 220-479 cDDD, HR, 0.706; 95% CI, 0.485-1.028; ≥ 480 cDDD, HR, 0.319; 95% CI, 0.118-0.863).

CONCLUSIONS: Metformin use in the initial 2 years was associated with a decreased risk of TB, and metformin users had a reduced risk compared with their sulfonylurea comparators.

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KEY WORDS: diabetes mellitus; metformin; prevention; sulfonylureas; TB

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ABBREVIATIONS: aDCSI = adapted diabetes complication severity index; AMPK = adenosine monophosphate-activated protein kinase; cDDD = cumulative defined daily dose; CKD = chronic kidney disease; DM = diabetes mellitus; ICD-9-CM = International Classification of Diseases; 9th Revision = Clinical Modification; LHID = Longitudinal Health Insurance Database; LTBI = latent TB infection; NHRID = National Health Insurance Research Database; T2DM = type 2 diabetes mellitus

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TB is a global infectious disease caused by *Mycobacterium tuberculosis* and remains one of the top 10 causes of death worldwide.[1] Latent TB infection (LTBI) may progress to active disease, especially in high-risk populations with immunosuppression.[2] Diabetes mellitus (DM), an immune dysfunction metabolic disease affecting 8.5% of the world population, carries a threefold increased risk for TB in these patients over patients without DM.[1,3,4] Among patients diagnosed with TB, DM is a prevalent comorbidity and increases the risk of poor outcomes, including treatment failure, relapse, and death.[5,6] Most previous studies aimed to improve outcomes in patients with DM acquiring active TB by extending the duration of anti-TB treatment, ensuring adherence, and discovering potential therapies.[7-9] However, for this high-risk population, information on reducing TB development is limited.[1,10]

Patients with DM and poor glycemic control have a higher risk of TB developing than do those with better control.[11] For type 2 DM (T2DM), metformin and the sulfonylureas are two of the most commonly used initial antidiabetic agents worldwide, and their effects on glycemic control are similar, although metformin is preferred because of the lower hypoglycemia rate and additional cardiovascular benefits.[12-15] In addition, metformin has been considered as a potential candidate drug against TB in in vitro and animal studies.[9] Recently, a case-control study reported that metformin treatment was associated with a lower chance of active TB in patients with DM, although the underlying mechanisms and interaction with glycemic control remain unclear.[16] However, even though metformin and sulfonylureas are both widely used as initial antidiabetic agents in patients with T2DM without advanced chronic kidney disease (CKD),[17] the beneficial effects and superiority of these two drugs in reducing TB risk among patients with T2DM remain unknown.

To this end, it is worthwhile to compare the impact of metformin and the sulfonylureas on the risk of TB using a large-scale cohort study. The findings could allow physicians to make better choices for TB prevention in high-risk patients with T2DM. Thus, we conducted a population-based cohort study to investigate the effect of metformin vs sulfonylureas on TB risk in patients with T2DM.

Methods

Data Source and Patients

This retrospective nationwide population-based cohort study was conducted in Taiwan using the Longitudinal Health Insurance Database (LHID)-2005, a data subset of the National Health Insurance Research Database (NHIRD), which included the data of 1 million random samples from all the beneficiaries with registration in 2005. The specifics of NHIRD and the accuracy of the major diagnosis codes are described elsewhere.[18,19] This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2015-04-004AC), and informed consent was not required for this study using deidentified secondary data.

Patients with a diagnosis of T2DM (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 250.x0 and 250.x2) that presented in one inpatient record or four or more outpatient records during 2003 to 2013 were identified.[19] The diagnosis of T2DM was validated by the prescription of oral antidiabetic agents or insulin injection, or both. Exclusion criteria included the following: age < 20 years, an antecedent history of type 1 DM (ICD-9-CM codes 250.x1 and 250.X3), CKD (ICD-9-CM code 585),[20] TB, and a diagnosis of T2DM made before 2003. Because advanced CKD, a risk factor for TB, is a contraindication for the use of metformin and most of the sulfonylureas, patients with underlying CKD were excluded to avoid selection bias.[17,21] To assess the dose effects of target drugs prescribed in the initial 2 years, only participants with ≥ 2 years of follow-up were included. Because people with a T2DM diagnosis prior to 2003 may have died before 2005 and had no chance to be randomly sampled into the LHID-2005, despite having ≥ 2 years of follow-up, all subjects with a T2DM diagnosis prior to 2003 were excluded to avoid unbalanced selection. Additionally, because statin drugs are associated with a reduced risk of TB, as previously reported,[22,23] patients who used statin drugs (> 15 cumulative defined daily dose, cDDD) before the index dates were excluded to minimize confounding factors. The index date was the date of first-time T2DM diagnosis. The included patients with T2DM were observed from the index date to the end points, namely, the occurrence of TB, withdrawal from the national health insurance system, and December 31, 2013.

Outcomes and Measurement

The outcome was TB occurrence (codes 010-018 in ICD-9-CM) validated by the prescription of at least two anti-TB drugs for > 28

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