CHEST

Optimal Duration of Anti-TB Treatment in Patients With Diabetes

Nine or Six Months?

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BACKGROUND: Diabetes mellitus (DM) increases the risk of TB recurrence. This study investigated whether 9-month anti-TB treatment is associated with a lower risk of TB recurrence within 2 years after complete treatment than 6-month treatment in patients with DM with an emphasis on the impact of directly observed therapy, short course (DOTs).

METHODS: Patients with pulmonary but not extrapulmonary TB receiving treatment of 173 to 277 days between 2002 and 2010 were identified from the National Health Insurance Research Database of Taiwan. Patients with DM were then selected and classified into two groups based on anti-TB treatment duration (9 months vs 6 months). Factors predicting 2-year TB recurrence were explored using Cox regression analysis.

RESULTS: Among 12,688 patients with DM and 43,195 patients without DM, the 2-year TB recurrence rate was 2.20% and 1.38%, respectively ($P < .001$). Of the patients with DM, recurrence rate decreased from 3.54% to 1.19% after implementation of DOTs ($P < .001$). A total of 4,506 (35.5%) were classified into 9-month anti-TB treatment group. Although a 9-month anti-TB treatment was associated with a lower recurrence rate (hazard ratio, 0.76 [95% CI, 0.59-0.97]), the benefit disappeared (hazard ratio, 0.69 [95% CI, 0.43-1.11]) under DOTs. Other predictors of recurrence included older age, male sex, malignancy, earlier TB diagnosis year, culture positivity after 2 months of anti-TB treatment, and anti-TB treatment being ≤ 80% consistent with standard regimen.

CONCLUSIONS: The 2-year TB recurrence rate is higher in a diabetic population in Taiwan and can be reduced by treatment supervision. Extending the anti-TB treatment by 3 months may also decrease the recurrence rate when treatment is not supervised.

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ABBREVIATIONS: CDC = Centers for Disease Control; DM = diabetes mellitus; DOTs = directly observed therapy, short course; DST = drug susceptibility test; HbA1c = glycated hemoglobin; HR = hazard ratio; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; NHIRD = National Health Insurance Research Database

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TB, a global public health threat, is still one of the leading causes of death among infectious diseases, especially in developing countries.[1] With the current standard of four combined drugs for 6 months, anti-TB treatment can cure most patients with TB, with a 2-year recurrence rate of 2% to 3%.[2,3] The recurrence rate can be further reduced by implementing the policy of directly observed therapy, short course (DOTs).[4] Although recurrence does occur, extended treatment of > 6 months is mainly recommended for extrapulmonary TB, drug-resistant TB, or when the regimen is modified because of adverse events, treatment failure, or nonadherence.[5]

The prevalence of diabetes mellitus (DM) is increasing worldwide, especially in Asia,[6] where TB is also highly endemic.[1] Numerous studies have presented convincing biologic evidence supporting the causal relationship of DM and impaired host immunity to TB.[7-9] In Taiwan, DM is the most common systemic comorbidity of patients with TB (18.3%-22.1%).[10] In a meta-analysis, the relative risk of TB recurrence in patients with DM compared with those without DM was 3.89 (95% CI, 2.43-6.23).[11] Given the increased recurrence rate in this special population, it is imperative to know whether increasing the duration of anti-TB treatment will reduce the recurrence rate, especially after implementation of DOTs. However, there is paucity of studies focusing on this issue, perhaps because such studies require large cohorts with long-term follow-up.

As the mandatory universal health insurance program offering comprehensive medical care coverage, the National Health Insurance of Taiwan has covered up to 99% of residents in Taiwan since 1996.[12] With a longitudinal follow-up of > 22 million subjects, the National Health Insurance Research Database (NHIRD) provides suitable research material to explore the impact of medical intervention on the outcome of special populations with long-term diseases. During the period since 2006, DOTs has been implemented in Taiwan. Thus, this study was conducted using the NHIRD to investigate the risk factors of TB recurrence in patients with DM, with special emphasis on the impact of anti-TB treatment duration and DOTs.

Materials and Methods

The institutional review board of National Taiwan University Hospital, Taipei, Taiwan approved this study (NTUH REC: 201112111RIC). As a retrospective study using an encrypted database, the institutional review board waived the need for informed consent.

Case Selection

Patients with pulmonary and without extrapulmonary TB diagnosed from 1996 to 2010 were identified (Fig 1). Those who were diagnosed after January 1, 2002 were selected because comprehensive data on mycobacteriology studies, including acid-fast smear, mycobacterial culture, identification, and drug susceptibility test (DST), were available in NHIRD since then. Given that drug-resistant TB, especially multidrug-resistant TB, was usually treated for > 9 months, only patients who received anti-TB regimen with a duration between 173 and 277 days were selected. Patients were also excluded if they received any non-first-line anti-TB drugs for > 14 days, to avoid inclusion of patients with drug-resistant TB or adverse reaction due to first-line anti-TB drugs. Patients were classified into two groups according to their treatment duration (6 vs 9 months) using 225 days as the cutoff.

The primary research outcome was TB recurrence, defined as recurrent episode of active TB within 2 years after completion of anti-TB treatment of the first episode of TB.[1] Patients were followed up for 2 years after completion of anti-TB treatment, until TB recurrence, December 31, 2010, or withdrawal of health insurance.

Definition of Active TB

Active pulmonary TB was defined by at least two ambulatory visits or one inpatient record with a compatible diagnosis, plus at least one prescription of three or more anti-TB drugs and prescriptions of at least two anti-TB drugs simultaneously for ≥ 120 days within a period of 180 days (e-Appendix 1).[13] Because there was no culture result in the NHIRD, DST ordered after 2 months of anti-TB treatment was used as a proxy for culture positivity after 2 months of anti-TB treatment under the assumption that DST was always done for all positive culture after 2 months of treatment.[14] Anti-TB treatment was considered > 80% consistent with standard regimen if isoniazid, rifamycin, ethambutol, and pyrazinamide were given for > 48 days in the first 2 months and isoniazid and rifamycin for > 144 days in the first 6 months of anti-TB treatment. The date of complete treatment was defined as the last date of simultaneous intake of two or more anti-TB drugs and without further anti-TB treatment in the next 60 days. Because it is difficult to correctly determine the outcome of anti-TB treatment other than complete treatment, the number of TB cases with complete anti-TB treatment within 1 year identified in the NHIRD was verified with that reported from the Taiwan Centers for Disease Control (Taiwan CDC).

Definition of DM

Patients were considered as having DM if they had at least one hospital admission or three (or more) outpatient visits with a DM diagnostic code (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 250 and A-code A181) within 1 year.[15] To avoid including women with gestational diabetes who returned to normoglycemia after child delivery, diabetes visit claims within 270 days before parturition were excluded.[16] Chronic DM complications were identified by at least three ambulatory or inpatient visits with a compatible ICD-9-CM code (diabetic nephropathy 250.4; diabetic retinopathy 250.5; diabetic vasculopathy 250.6; diabetic neuropathy 250.7; and other diabetic complications 250.8 and 250.9).

Comorbidity and Income Status

Underlying comorbidities and low income were noted if they were present before the diagnosis of pulmonary TB according to previous publications (e-Appendix 1).[13,17] AIDS was defined by at least two outpatient visits within a period of 180 days, or one inpatient record, or prescription of antiretroviral agents with compatible diagnoses (ICD-9-CM code 042-44 or V08).

Statistical Analysis

Correlation between case numbers in the NHIRD and Taiwan CDC were calculated by using Pearson correlation. Because of limited follow-up period, case numbers in 2010 were not considered in correlation analysis. Intergroup difference was calculated using independent-sample *t* test for continuous variables and the χ-square test or Fisher exact test for categorical variables, as appropriate.

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