Nation-based case-control study investigating the relationship between oral corticosteroids use and pulmonary tuberculosis

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ABSTRACT

Background and objective: No published formal study focuses on the relationship between oral corticosteroids use and pulmonary tuberculosis in Taiwan. The aim of the study was to investigate whether oral corticosteroids use was associated with increased odds of pulmonary tuberculosis.

Methods: The retrospective, nation-based, case-control study was conducted to analyze the database of the Taiwan National Health Insurance Program between 2000 and 2013. Subjects aged 20 to 84 years with newly diagnosed pulmonary tuberculosis were defined as the cases (n = 6021). Randomly selected subjects without pulmonary tuberculosis aged 20 to 84 years were defined as the controls (n = 6021). Subjects who never had a prescription for oral corticosteroids were defined as never use. Subjects who ever had a prescription for oral corticosteroids were defined as ever use.

Results: After adjustment for confounders, the adjusted odds ratio of pulmonary tuberculosis was 1.91 for subjects with even use of oral corticosteroids (95% confidence interval 1.73, 2.11), comparing with never use. The adjusted odds ratio of pulmonary tuberculosis was 1.03 for subjects with increasing cumulative dose of oral corticosteroids for per milligram (95% confidence interval 1.02, 1.03), comparing with never use. In addition, the adjusted odds ratios of pulmonary tuberculosis were 1.83 (95% CI 1.65, 2.02) for subjects with cumulative duration of oral corticosteroids < 3 months, and 2.12 (95% CI 1.87, 2.40) for subjects with cumulative duration ≥ 3 months, comparing with never use.

Conclusion: Though the finding is not unexpected, use of oral corticosteroids is significantly associated with 1.9-fold increased odds of pulmonary tuberculosis, independent of other risk comorbidities. There are dose-dependent and duration-dependent effects of oral corticosteroids use on the risk of pulmonary tuberculosis.

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1. Introduction

Tuberculosis remains one of the deadliest infectious diseases worldwide. WHO reported that there were about 9.0 million people developing tuberculosis and 1.5 million people dying from this disease in 2013 [1]. Current evidence indicates that numerous risk factors are found to be associated with development of pulmonary tuberculosis, including smoking, diabetes mellitus, malnutrition, alcoholism, human immunodeficiency virus infection, and living or working in crowded space [2–4].

Current evidence indicates that use of corticosteroids is associated with the increased susceptibility to tuberculosis due to its inhibition of immune functions [5–7]. In Liao et al.'s study in Taiwan, the overall incidence of tuberculosis was 68 per 100,000 population from 2004 to 2008 [8]. To date, no published formal study focuses on the relationship between use of oral corticosteroids and pulmonary tuberculosis in Taiwan. Given that tuberculosis remains a high prevalence in Taiwan, we make a rational hypothesis that use of oral corticosteroids may be associated with increased risk of pulmonary tuberculosis in Taiwan. If the relationship is positive, physicians should be aware of the potential risk of pulmonary tuberculosis in patients with use of oral corticosteroids. Therefore, a nation-based, retrospective, case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program to investigate whether (1) use of oral corticosteroids was

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associated with increased odds of pulmonary tuberculosis; (2) there were dose-dependent and duration-dependent effects of oral cortico-steroids use on the risk of pulmonary tuberculosis?

2. Methods

2.1. Data source and study design

Taiwan is an independent country with >23 million persons. The Taiwan National Health Insurance Program launched in March 1995, and now it has covered around 99% of the persons living in Taiwan [9]. The details of the program have been written in previous studies [10–14]. A nation-based, retrospective, case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115).

2.2. Selection of cases and controls

We selected subjects aged 20 to 84 years with newly diagnosed pulmonary tuberculosis (the International Classification of Diseases (ICD) 9th Revision, ICD-9 codes 010, 011, 012, and 018) between 2000 and 2013 as the cases with pulmonary tuberculosis. The index date was defined as the date of cases being diagnosed with pulmonary tuberculosis. We randomly selected subjects without pulmonary tuberculosis aged 20 to 84 years from the same database as the controls. Both cases and controls were matched with sex, age (every 5-year interval), comorbidities, and the year of index date (Fig. 1).

2.3. Potential confounders

Some medical conditions which could be related to pulmonary tuberculosis were included as follows: alcohol-related disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, human immunodeficiency virus infection, gastrectomy, pneumoconiosis, as well as chronic liver disease including cirrhosis, hepatitis

B infection, hepatitis C infection, and other chronic hepatitis. To increase the validity of analysis, subjects who had the same diagnosis for 3 consecutive clinical visits in the ambulatory care and/or one episode of hospitalization diagnosis could be included in the study. Principal diagnosis and secondary diagnosis were used equally. Therefore, pulmonary tuberculosis and other medical conditions were documented for 3 or more records in the ambulatory care and/or one record during hospitalization. All comorbidities were diagnosed according to ICD-9 codes. The accuracy of ICD-9 codes has been validated in previous studies [10–20].

2.4. Assessment of corticosteroids exposure

It is relatively difficult to calculate the doses of topical corticosteroids use or inhaled corticosteroids use. It is also very rare for patients with long-term use of injected corticosteroids at outpatient department. In order to quantify the dosage, only oral corticosteroids were included for detailed analysis. Topical, inhaled, and injected corticosteroids were collected together as other forms of corticosteroids for adjustment. Oral corticosteroids in Taiwan were available as follows: cortisone, dexamethasone, fludrocortisone, methylprednisolone, prednisolone, and triamcinolone. To investigate the relationship between oral corticosteroids use and pulmonary tuberculosis, prescription history of oral corticosteroids before the index date was included. To diminish the biased results, subjects whose final prescriptions for oral corticosteroids were filled >-12 months before the index date were excluded from the study. Therefore, only subjects whose final prescriptions for oral corticosteroids were filled within 12 months before the index date were included. Subjects who never had a prescription for oral corticosteroids were defined as never use. Those who ever had a prescription for oral corticosteroids were defined as ever use.

2.5. Statistical analysis

Distributions of sex, age, oral corticosteroids use, other forms of corticosteroids use, and comorbidities between the cases and controls were compared by the Chi-square test for categorized variables, and the *t*-test
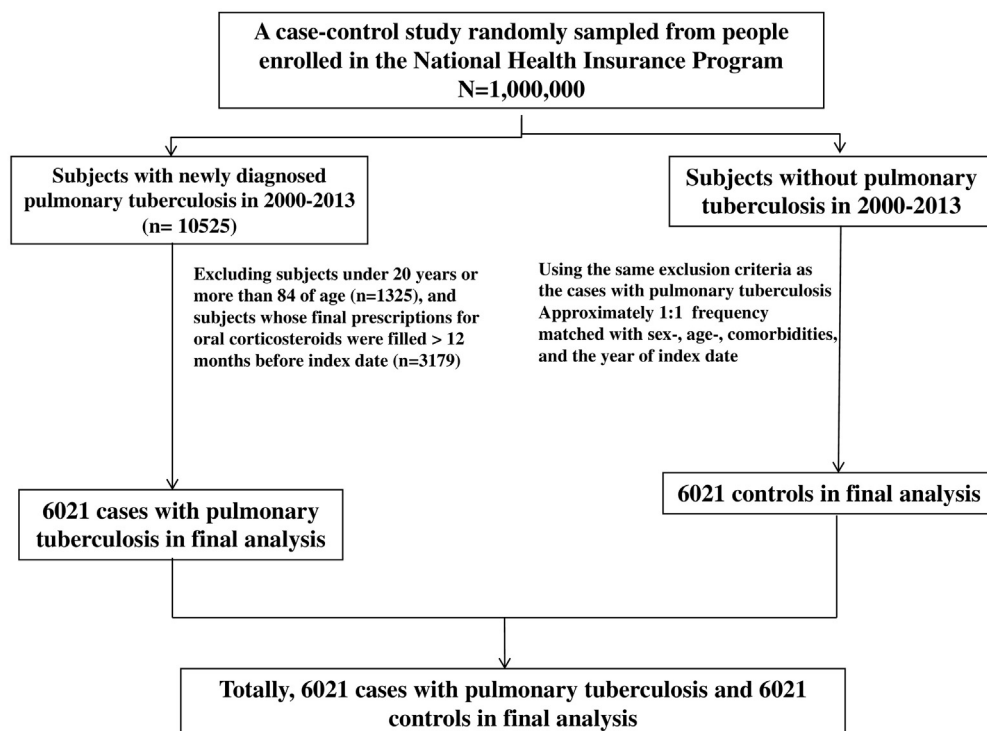

Fig. 1. Flow diagram of the study revealing the selection of cases with pulmonary tuberculosis and controls.