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Original Article

The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis

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Abstract

Background: Anti-tuberculosis drug-induced liver injury (ATDILI) is a major safety concern in the treatment of tuberculosis (TB). The impact of chronic hepatitis C (CHC) infection on the risk of ATDILI is still controversial. We aimed to assess the influence of CHC infection on ATDILI through a systematic review and meta-analysis.

Methods: We systemically reviewed all English-language literature in the major medical databases with the subject search terms "anti-tuberculosis drug-induced liver injury" and "anti-tuberculosis drug-induced hepatotoxicity". We then performed a systematic review and meta-analysis of the papers relevant to hepatitis C in qualified publications.

Results: A total of 14 studies were eligible for analysis, which included 516 cases with ATDILI and 4301 controls without ATDILI. The pooled odds ratio (OR) of all studies for CHC infection to ATDILI was 3.21 (95% confidence interval (CI): 2.30−4.49). Subgroup analysis revealed that the CHC carriers had a higher risk of ATDILI than those without CHC both in Asians (OR = 2.96, 95% CI: 1.79−4.90) and Caucasians (OR = 4.07, 95% CI: 2.70−6.14), in those receiving standard four combination anti-TB therapy (OR = 2.94, 95% CI: 1.95−4.41) and isoniazid monotherapy (OR = 4.18, 95% CI: 2.36−7.40), in those with a strict definition of DILI (serum alanine aminotransferase [ALT] > 5 upper limit of normal value [ULN], OR = 2.59, 95% CI: 1.58−4.25) and a loose definition of DILI (ALT > 2 or 3 ULN, OR = 4.34, 95% CI: 2.96−6.37), and in prospective studies (OR = 4.16, 95% CI: 2.93−5.90) and case−control studies (OR = 2.43, 95% CI: 1.29−4.58).

Conclusion: This meta-analysis suggests that CHC infection may increase the risk of ATDILI. Regular liver tests are mandatory for CHC carriers under anti-TB therapy.

Keywords: Anti-tubercular agent; Anti-Tuberculosis drug-induced liver injury; Drug-induced liver injury; Hepatitis C; Meta-analysis; Tuberculosis

1. Introduction

Tuberculosis (TB) remains a major health problem worldwide. Drug-induced liver injury (DILI) is one of the most common adverse effects of anti-TB medication and is associated with the three major first-line drugs: isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA).[1−4] Anti-tuberculosis drug-induced liver injuries (ATDILIs) range from asymptomatic elevation of aminotransferase to clinical hepatitis, and they can be fatal.[1,2] The incidence of ATDILI

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depends on the regimen used, the definition of DILI, and many other factors.[1−4]

Old age, female gender, human immunodeficiency virus (HIV) infection, abnormal baseline liver function tests, chronic alcohol drinking, chronic hepatitis B and C infections, and genetic factors have been proposed to be risk factors for ATDILI.[1−4] Our previous studies showed that genetic polymorphisms of some drug-metabolizing enzymes may be associated with ATDILI.[3,4] Furthermore, chronic hepatitis B infection has been reported to potentially increase the risk and severity of ATDILI, especially in Asians.[5] Similarly, some studies have suggested that chronic hepatitis C (CHC) infection may increase the incidence of ATDILI,[6−14] although other studies have not found an association between CHC infection and susceptibility to ATDILI.[15−19] The guidelines for anti-TB treatment in the USA, Taiwan and many other countries suggest screening for CHC infection status before starting treatment, and regular monitoring of liver biochemical tests in patients with CHC infection.[1,20] This recommendation is based on the belief that CHC infection can increase susceptibility to ATDILI. However, all of the relevant studies have a small sample size and variable results, and whether CHC infection can predispose to ATDILI is still unclear. Hence, we performed this systematic review and meta-analysis to assess the influence of CHC infection on the risk of ATDILI.

2. Methods

2.1. Identification and retrieval of studies

We conducted a literature search for English-language articles assessing the link between CHC infection and ATDILI published up to September 2016 in PubMed, Medline, Embase and the Cochrane Database of Systemic Reviews using the medical subject heading search terms “anti-tuberculosis drug-induced liver injury” and “anti-tuberculosis drug-induced hepatotoxicity”. Articles were selected for full text review based on the title and abstract. In addition, we manually searched the reference lists of the retrieved articles to increase the yield of potentially relevant articles. Only the papers relevant to hepatitis C were selected for systematic review and meta-analysis. Two researchers independently examined all papers and assessed their eligibility for this study. Discordant opinions were resolved by consensus with the other co-authors.

2.2. Inclusion and exclusion criteria

We included both prospective studies and retrospective case−control studies into the meta-analysis. The included studies had to fulfill the following selection criteria: (1) patients receiving standard anti-TB treatment including INH for active TB, or INH single drug prevention therapy for latent TB; (2) having data on patients with or without ATDILI, and with or without CHC infection; (3) serum anti-hepatitis C virus (HCV) antibody tested in all patients and controls; (4) studies with a clear definition of ATDILI, in which how many times of the upper normal limit of serum alanine aminotransferase (ALT) and/or serum total bilirubin were specified as DILI; (5) ATDILI was defined as at least more than two times the upper limit of normal value (ULN) of serum ALT or aspartate aminotransferase (AST); and (6) published as a full-length article. The exclusion criteria were: (1) studies with fewer than five patients with CHC infection; (2) repeated use of the same patient/control groups in the second paper; and (3) incomplete data on the number of cases, controls and percentage of positive anti-HCV. Studies included in the analysis were reviewed for the following characteristics: authors and year of publication; ethnicity; prospective or retrospective case−control study; anti-TB regimen; and definition of ATDILI.

2.3. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the incidence of ATDILI and CHC infection were calculated. Heterogeneity was assessed by between-study variance using I^2 statistics with a cutoff value of $\geq$50%, or the x^2 test for Cochran Q statistics with $p < 0.10$. If significant heterogeneity was found, a random effects model was selected to analyze the pooled data and subgroup analysis was performed. Funnel plots were used to assess publication bias. All statistical analyses were performed using Review Manager version 5.3.5 (RevMan for Windows, 2015; The Cochrane Collaboration, Oxford, UK).

3. Results

A total of 421 citations were retrieved on the initial major database search, from which 14 studies were determined to be eligible for meta-analysis (Fig. 1). The baseline characteristics of the included studies are listed in Table 1. Of the patients who underwent anti-TB treatment, 516 cases with DILI and 4301 controls were enrolled into this analysis. Eight studies focused on Asians, four studies were derived from studies on Caucasian patients, and only one study focused on African American patients (Table 1). Nine of the 14 studies were prospective studies, and the other five were retrospective case−control studies. Ten of the studies focused on patients with active TB receiving ongoing standard treatment with four-drug combination therapy, and the other four studies enrolled patients with latent TB undergoing isoniazid single-drug prophylactic treatment. Seven studies adopted the strict definition of DILI as serum ALT more than five times the ULN, while the other seven studies used a loose definition of DILI (ALT or AST > 2 or 3 ULN).

The pooled OR of all studies for CHC infection to ATDILI was 3.21 (95% CI: 2.30−4.49, Fig. 2). Mild heterogeneity was noted among the studies (I^2 = 37%, p = 0.08). However, no significant publication bias was detected in funnel plot analysis (Fig. 3). Further subgroup analysis revealed that the CHC carriers had a higher risk of ATDILI than those without CHC both in Asians (OR = 2.96, 95% CI: 1.79−4.90) and Caucasians (OR = 4.07, 95% CI: 2.70−6.14, Fig. 4), in those

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