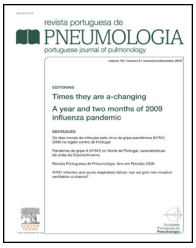
Rev Port Pneumol. 2015;21(3):144–150

revista portuguesa de PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org



ORIGINAL ARTICLE

Incidence and risk factors of major toxicity associated to first-line antituberculosis drugs for latent and active tuberculosis during a period of 10 years

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Received 2 May 2014; accepted 30 August 2014
Available online 7 March 2015

KEYWORDS
Tuberculosis;
Adverse reaction;
Antituberculosis;
Treatment

Abstract
Introduction: Adverse drug reactions (ADR) to first-line antituberculosis drugs are frequent and have important implications that may affect the effectiveness of treatment and course of tuberculosis (TB).
Material and methods: Retrospective data analysis of clinical records and national registration forms from patients with ADR to first line antituberculosis that occurred between 2004 and 2013 at a Portuguese Pulmonology Diagnostic Centre, and from a case–control population matched by sex, age and year of initiation of treatment.
Results: Of the 764 patients treated with antituberculosis drugs, 55 (52.7% male, 92.7% European, mean age 50.8 ± 19.5 years) had at least one severe ADR and six had a second ADR, for a total of 61 events. The most frequent ADR were hepatotoxicity (86.9%), rash (8.2%) and others, such as ocular toxicity, gastrointestinal intolerance and angioedema (4.9%). Isoniazid, alone or in combination, was the antituberculosis drug most associated to toxicity. Due to ADR, treatment time changed an average of 1.0 ± 2.6 months (range −3.4 to 10.6). There was no correlation between age or gender and the overall incidence of ADR although we found a significant association between younger age and an increased risk of hepatotoxicity ($P = 0.035$). There was also a statistically significant relationship between ADR and diabetes mellitus ($P = 0.042$) but not for other comorbidities or multi-resistant TB risk factors.
Conclusions: This study found a high frequency of ADR with strong impact on subsequent therapeutic orientation. What seems to be of particular interest is the relationship between ADR and diabetes mellitus and the increased frequency of hepatotoxicity in younger patients.

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http://dx.doi.org/10.1016/j.rppnen.2014.08.004

Introduction

The global burden of tuberculosis (TB) is currently still very high. It represents one of the major causes of infectious disease mortality despite the availability of curative treatment.[1] Moreover, latent tuberculosis infection (LTBI) affects over a third of the worldwide population posing a high risk for later reactivation of the disease. Therefore, TB chemotherapy is essential as an intention-to-cure measure and also as a public health policy to prevent *Mycobacterium tuberculosis* transmission.

Portugal remains the only country in Western Europe with an intermediary-prevalence of tuberculosis.[1] In 2012 alone, a total of 2399 new cases of TB were reported, for an estimated 22.8 cases per 100,000 inhabitants, while 157 patients died of TB while on treatment.[2]

TB disease is treated with multiple effective drugs combined for a long period of time that extends for a minimum of 6 months, but in special circumstances there is demand for longer treatments.[3,4] Treatment completion, defined by the number of doses taken over a period of time, is vital to prevent treatment failure, relapse and development of resistance.

Four drugs form the core of treatment regimens for drug-susceptible organisms: PZA, isoniazid (INH), rifampicin (RIF) and ethambutol (EMB). All of these first-line drugs can induce mild to severe adverse drug reactions (ADR), including: hepatotoxicity associated to INH, RIF and PZA; cutaneous reactions associated to INH, PZA and EMB; gastrointestinal intolerance to RIF; and retrobulbar neuritis related to EMB.[5–7] Since streptomycin (SM) was no longer considered a first-line drug there was a diminished incidence of ototoxicity, its main side effect.[8] Regarding latent tuberculosis infection (LTBI), standard regimens as, for example, short-courses of INH plus RIF are associated with an increased risk for ADR such as hepatotoxicity.[7,9,10]

When an ADR occurs, especially when severe, one or more drugs may have to be discontinued or treatment interrupted, which has multiple implications, particularly extended treatment time and an increased risk for drug resistance, treatment failure and relapse. In addition, use of alternative regimens are also related to important side effects and pose compliance issues. All patients must be closely monitored to immediately recognize major ADR and activate proper therapeutic measures.

Material and methods

Patient selection and follow-up

Between 2004 and 2013, all patients who experienced major ADR due to first-line antituberculosis drugs provided on ambulatory basis by our Pulmonology Diagnostic Centre (PDC) were identified and all demographic and clinical data were retrospectively collected. Data from a group control consisting of a matched population by sex, age and year of initiation of treatment were also assembled for comorbid conditions analysis.

Inclusion criteria were as follows: age of 17 years or older; established diagnosis of active TB, either pulmonary or extrapulmonary, or proven LTBI; treatment regimen with first-line antituberculosis drugs; confirmed ADR to at least one of the antituberculosis drugs.

TB was defined as a clinically compatible illness confirmed by microbiological analysis or, when negative, a case with compatible clinical, radiologic, and/or histologic findings, and exhibiting positive response to treatment. LTBI was defined by the absence of clinical features suggestive of TB, normal chest radiographic examination and a positive tuberculin skin test (TST) induration. Since 2008, after the acquisition of laboratory means to perform the interferon gamma release assay (IGRA) using the ELISA method (Quantiferon-TB® Gold In-tube), this highly specific test was implemented as an active screening routine to confirm all positive TST reactions from patients suspected of having TB infection and support treatment decision.

Once having started antituberculosis treatment, all patients were closely monitored for surveillance of possible ADR and other disease-related complications. The first appointment occurred 15 days after beginning treatment, the second appointment at 1-month of treatment and the following ensued at monthly intervals.

Blood tests including complete blood count (CBC), liver transaminases, bilirubin (total and partial) and creatinine, were routinely checked at 15, 30 and 60 days of treatment and, afterwards, once each 2 months until the treatment was completed. Viral serology for hepatitis and HIV were routinely assessed, mostly before starting antituberculosis treatment.

Whenever necessary, as in the event of a serious side effect or complication, the patient was consulted or serum analyses were done beyond the usual routine. Also, if required, other complementary studies were added to the standard evaluation.

From patient's clinical records and national registration forms, information was collected regarding sex, age, nationality, residency, career occupation, symptoms, risk factors such as intravenous drug abuse, alcoholism or residence in a social support community, comorbidities, site of disease, diagnostic tests, initial treatment, adverse effects and outcomes.

Major ADR were defined as those that required discontinuation of one or more drugs, shift to second-line drugs or hospital admission. When all drugs were suspended, they were restarted after clinical and/or laboratory complete resolution, in a sequential way to possibly isolate the drug that caused the toxicity. A second-line treatment was initiated when a slow resolution was anticipated or treatment interruption was not desirable.

Hepatitis was defined as liver transaminases more than three times higher than the upper limit of normal in the presence of symptoms such as nausea, vomiting or abdominal pain, or transaminases more than five times the upper limit of normal without symptoms.

Significant episodes of cutaneous toxicity related to extensive eruption, symptoms like fever and mucous membrane involvement, or to sustained complaints while on medication with anti-histaminic drugs.

Gastrointestinal disturbance was considered major when there was no improvement despite measures such as combining the timing of administration to main meals or proton pump inhibitor medication.