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Review

Efficacy and safety of a four-drug fixed-dose combination regimen versus separate drugs for treatment of pulmonary tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Introduction: Tuberculosis, particularly multi-drug-resistant tuberculosis, is a major cause of morbidity and mortality worldwide. To the best of our knowledge, however, no study to date has assessed the combined use of the four available drugs for tuberculosis treatment, which is an issue of great clinical relevance.
Objective: To determine whether the four-drug fixed-dose combination is safer or more effective than separate drugs for treatment of pulmonary tuberculosis.
Methods: A systematic review of the literature was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
Results: In pooled results from five randomized controlled trials with 3502 patients across Africa, Asia, and Latin America, four-drug fixed-dose combination therapy was no better than separate drugs therapy in terms of culture conversion after 2 and 6 months of treatment. There were no significant differences between the groups in overall incidence of adverse effects. However, the meta-analytic measure (log odds ratio) revealed that separate drugs treatment had a 1.65 [exp (0.5) = 1.65] increased chance of gastrointestinal adverse effects compared to four-drug fixed-dose combination treatment.
Conclusions: The reviewed studies showed that four-drug fixed-dose combination therapy provides greater patient comfort by reducing the number of pills and the incidence of gastrointestinal adverse effects, as well as simplifying pharmaceutical management at all levels.

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Introduction

Tuberculosis (TB) continues to be a major cause of morbidity and mortality worldwide, with 9 million new cases of TB diagnosed and 1.5 million TB-related deaths recorded globally in 2013. Approximately 95% of the estimated numbers of TB cases occur in low-income countries, with 82% of these cases being concentrated in 22 countries, among which Brazil ranks 17th.[1] This TB burden is increased by human immunodeficiency virus (HIV) infection, which impairs the immune system and allows progression to active TB disease in large numbers of people.[2]

Furthermore, the global burden of drug-resistant TB is growing. In 2010, an estimated 650,000 cases of drug-resistant TB were reported worldwide.[3] Incidence of drug-resistant TB has been on the rise in Brazil, according to data obtained in the Second Brazilian National Survey on Anti-TB Drug Resistance 2007–2008.[4] In 2014, the Brazilian Ministry of Health delivered 148 GeneXpert instrument systems to all 92 municipalities that comprise the Rapid TB-Test Network, which covers all Brazilian states. These instrument systems are capable of diagnosing TB in 2 h, while simultaneously identifying the sensitivity profile to rifampicin, one of the main drugs for TB treatment.[5] Alongside the rising prevalence of drug-resistant TB, there has been an increase in the spread of cases due to direct contact with drug-resistant TB patients. Consequently, drug-resistant TB has become an epidemic itself, especially in high-burden settings.[6,7] Multidrug resistance is a further threat to TB control. Development of drug- or multi-drug-resistant (MDR) TB is caused by inadequacies in treatment, such as in the number of drugs in the regimen to which the bacilli are susceptible, the dose or dosing frequency, the drug quality, or the treatment adherence.[3,8,9]

Fixed-dose combinations (FDCs) of drugs for TB treatment have been advocated internationally to prevent the emergence of drug resistance attributable to inappropriate drug intake.[10,11] Use of FDCs can reduce the risk of an incorrect dosage, simplify drug procurement, and aid in ensuring adherence without changing the drug dosage. In 2010, Brazil's National TB Program altered their traditional anti-TB treatment (2RHZ/RH regimen), which comprised rifampicin (R), isoniazid (H), and pyrazinamide (Z) for 2 months followed by R and H for 4 months. The change followed a report by the Second Brazilian National Survey on Anti-TB Drug Resistance (2007–2008), which showed that primary resistance to H or H + R had increased from 4.4% to 6.0% and from 1.1% to 1.4%, respectively, compared to data from the First Brazilian Survey (1995–1997). In the new 2RHZE/4RH regimen, a fourth drug, ethambutol (E), was added to the intensive phase (first 2 months) of TB treatment. Capsules containing R and H, administered with Z tablets, were replaced by FDC tablets containing R, H, Z, and E. In the new formulation, H and Z were administered at lower doses compared to the traditional 2RHZ/RH regimen. Pharmacological presentation of this scheme is a tablet containing a FDC of four drugs: 150 mg of R, 75 mg of H, 400 mg of Z, and 275 mg of E. The 2RHZE/RH scheme is still recommended for children under 10 years of age.[4]

The basic treatment of TB with four drugs is used worldwide, showing excellent effectiveness, particularly among patients with good treatment adherence. With the addition of a fourth drug, it is expected that treatment success will improve, preventing any further increase in resistance to H with or without R. FDC regimens have advantages such as improved patient comfort and treatment adherence (by reducing the number of pills) and simplified pharmaceutical management at all levels.[4] The aims of this new approach were to increase treatment adherence and prevent drug resistance.[12]

Over the years, problems have been found with the quality of the 2RHZE/4RH regimen, such as a reduced bioavailability of R, instability of the formulation, toxic/allergic AEs, and development of resistance. Several studies have been conducted to assess the bioavailability, acceptability, and microbiological efficacy of R and H, with or without Z, administered as a FDC for daily or intermittent use.[13–17] However, in patients with newly diagnosed TB, the use of four drugs in a fixed-dose combination (4-FDC) in the first 2 months of treatment has not been assessed for safety and efficiency relative to the administration of separate drugs (SDs).

To frame recent studies within the broader evidence base, we systematically reviewed randomized clinical trials (RCTs) that provided clinical data regarding the efficacy and safety of 4-FDC drugs in the treatment of pulmonary TB. This study aimed to determine whether the administration of 4-FDC is safer or more effective than SD regimens for the treatment of pulmonary TB.

Methods

A systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The protocol for this review was recorded on 23 May 2013 in the International Register of Prospective Systematic Reviews (PROSPERO) under registration no. CRD42013003217.

Search strategy and selection criteria

Articles were searched in the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL – http://www.cinahl.com), Cochrane Library (http://www.update-software.com/cochrane), Latin American and Caribbean Literature in Health Sciences (LILACS; http://lilacs.bvsalud.org/), MEDLINE (http://www.nlm.nih.gov), Scientific Electronic Library Online (SciELO; http://www.scielo.br), Scopus (http://www.scopus.com), Web of Science (http://www.webofknowledge.com), Science Direct (http://www.sciencedirect.com), ExcerptaMedica Database (EMBASE; http://www.embase.com), CAPES Theses Database, and public domain internet databases (http://www.periodicos.capes.gov.br). All databases were searched from inception through 10 September 2013 for articles in English, French, and Spanish. We sought to compare results from RCTs involving patients with newly diagnosed TB who were administered a 4-FDC or SD regimen in the first 2 months of treatment for pulmonary TB. Therefore, a search strategy was developed by combining the following search terms: *tuberculosis*; *treatment*; and *rifampicin*; and *isoniazid*; and *ethambutol*; and *pirazinamide*;

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