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WILEY

[Intervention Review]

Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis

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ABSTRACT

Background

People who are newly diagnosed with pulmonary tuberculosis (TB) typically receive a standard first-line treatment regimen that consists of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by four months of isoniazid and rifampicin. Fixed-dose combinations (FDCs) of these drugs are widely recommended.

Objectives

To compare the efficacy, safety, and acceptability of anti-tuberculosis regimens given as fixed-dose combinations compared to single-drug formulations for treating people with newly diagnosed pulmonary tuberculosis.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL, published in the Cochrane Library, Issue 11 2015); MEDLINE (1966 to 20 November 2015); EMBASE (1980 to 20 November 2015); LILACS (1982 to 20 November 2015); the metaRegister of Controlled Trials; and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), without language restrictions, up to 20 November 2015.

Selection criteria

Randomized controlled trials that compared the use of FDCs with single-drug formulations in adults (aged 15 years or more) newly diagnosed with pulmonary TB.

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Data collection and analysis

Two review authors independently assessed studies for inclusion, and assessed the risk of bias and extracted data from the included trials. We used risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data with 95% confidence intervals (CIs). We attempted to assess the effect of treatment for time-to-event measures with hazard ratios and their 95% CIs. We used the Cochrane 'Risk of bias' assessment tool to determine the risk of bias in included trials. We used the fixed-effect model when there was little heterogeneity and the random-effects model with moderate heterogeneity. We used an I^2 statistic value of 75% or greater to denote significant heterogeneity, in which case we did not perform a meta-analysis. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We included 13 randomized controlled trials (RCTs) in the review, which enrolled 5824 participants. Trials were published between 1987 and 2015 and included participants in treatment with newly diagnosed pulmonary TB in countries with high TB prevalence. Only two trials reported the HIV status of included participants.

Overall there is little or no difference detected between FDCs and single-drug formulations for most outcomes reported. We did not detect a difference in treatment failure between FDCs compared with single-drug formulations (RR 1.28, 95% CI 0.82 to 2.00; 3606 participants, seven trials, *moderate quality evidence*). Relapse may be more frequent in people treated with FDCs compared to single-drug formulations, although the confidence interval (CI) includes no difference (RR 1.28, 95% CI 1.00 to 1.64; 3621 participants, 10 trials, *low quality evidence*). We did not detect any difference in death between fixed-dose and single-drug formulation groups (RR 0.96, 95% CI 0.67 to 1.39; 4800 participants, 11 trials, *moderate quality evidence*).

When we compared FDCs with single-drug formulations we found little or no difference for sputum smear or culture conversion at the end of treatment (RR 0.99, 95% CI 0.96 to 1.02; 2319 participants, seven trials, *high quality evidence*), for serious adverse events (RR 1.45, 95% CI 0.90 to 2.33; 3388 participants, six trials, *moderate quality evidence*), and for adverse events that led to discontinuation of therapy (RR 0.96, 95% CI 0.56 to 1.66; 5530 participants, 13 trials, *low quality evidence*).

We conducted a sensitivity analysis excluding studies at high risk of bias and this did not alter the review findings.

Authors' conclusions

Fixed-dose combinations and single-drug formulations probably have similar effects for treating people with newly diagnosed pulmonary TB.

23 April 2019

No update planned

Other

This is not a current research question.

PLAIN LANGUAGE SUMMARY

Fixed-dose combinations for treating pulmonary tuberculosis

What are fixed-dose combinations and how might they improve care of people with tuberculosis

Tuberculosis (TB) is an important health problem, especially in developing countries. The treatment for pulmonary TB in new patients includes four oral medicines taken for six months, sometimes as fixed-dose combinations (FDCs) that are combined in one tablet, or taken separately as single-drug formulations. The World Health Organization recommends prescribers use fixed-dose combinations to reduce the number of tablets that people take. On the supply side, this might reduce prescribing errors and improve drug supply efficiency; on the patient's side, FDCS simplify treatment and improve adherence.

We conducted a review to assess the efficacy, safety, and acceptability of FDCs compared with single-drug formulations for treating people with newly diagnosed pulmonary TB.

What the research says

We searched for relevant trials up to 20 November 2015, and included 13 randomized controlled trials that enrolled 5824 people. Trials were published between 1987 and 2015 and included participants in treatment with newly diagnosed pulmonary TB in countries with high TB prevalence. Only two trials reported the HIV status of included participants.

There is probably little or no difference in FDCs compared to single-drug formulations for treatment failure (*moderate quality evidence*); relapse may be more frequent (*low quality evidence*); and the number of deaths were similar (*moderate quality evidence*).

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There is little or no difference in sputum smear or culture conversion (*high quality evidence*), and no difference was shown for serious adverse events (*moderate quality evidence*) or adverse events that led to discontinuation of therapy (*low quality evidence*).

Authors' conclusions

We concluded that fixed-dose combinations have similar efficacy to single-drug formulations for treating people with newly diagnosed pulmonary TB.

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