Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis


CRD summary
This review concluded that treatment outcomes of tuberculosis treatment were significantly worse with shorter durations of rifampin. Treatment outcomes were similar across the different intermittent schedules evaluated but there was insufficient evidence for administration twice weekly throughout treatment. These conclusions reflected the results of the included trials, which included large numbers of patients, and appear likely to be reliable.

Authors' objectives
To assess the effect of duration and intermittency of rifampin use on treatment outcomes in tuberculosis.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1965 to June 2008 for published studies in English, French or Spanish. Search terms were reported. References of identified studies, recent systematic reviews, a review of all Medical Research Council trials and treatment guidelines were also checked.

Study selection
Randomised controlled trials (RCTs) of standardised treatment that included at least isoniazid and rifampin in patients with new cases of active, bacteriologically confirmed, tuberculosis were eligible for inclusion. Bacteriological confirmation could be by acid-fast bacilli smear microscopy and/or mycobacterial culture. Trials or trial arms that included rifapentine or rifabutin therapy, non drug therapy, or once-weekly or mono-drug therapy were all excluded from the review. Included trials were also required to use bacteriological confirmation of treatment failure or relapse. Detailed definitions of treatment failure and relapse were provided in the paper. Acquired drug resistance was also assessed.

All included trials enrolled adults. Only a small number of trials included human immunodeficiency virus (HIV) positive patients. The great majority of trials used rifampin at a dose of 600mg/d or 10 to12 mg/kg/d; a small number of trials did not report the dose or used 450mg/d. Approximately half of the trials used supervised treatment protocols.

Two reviewers independently assessed the studies for inclusion; disagreements were resolved through consensus or consultation with a third reviewer.

Assessment of study quality
Two reviewers assessed the trials for allocation concealment and method of randomisation, and for losses to therapy. Trials with fewer than 10% of patients lost to follow-up were considered to be high quality. Also considered high quality were trials using an appropriate method of allocation concealment.

Data extraction
Two reviewers independently extracted data on patient characteristics and treatment outcomes; disagreements were resolved through consensus. Patients with initial resistance to rifampin, including those with multi-drug resistance, were excluded from the analysis if they were identified in the report. Acquired resistance was included in the outcomes of treatment failure or relapse. A per-protocol approach to analysis was adopted.

Methods of synthesis
Trials considered to compare the same regimens (for definition of comparability see paper) were combined in a fixed-effect Mantel-Haenszel meta-analysis to calculate risk differences with 95% confidence intervals (CI). A subsequent indirect comparison was also performed to compare different treatment across trials using a binomial regression model, which included study as a random effect. In each case, heterogeneity was assessed using the $I^2$ statistic.
A priori subgroup analyses were used to assess: the impact of duration and scheduling of rifampin; initial drug resistance; use of pyrazinamide or streptomycin; number of susceptible drugs in the initial or continuation phase; supervision of therapy; proportion of smear-positive patients; and losses during the treatment phase.

Meta-regression using a negative binomial model was also used to investigate the impact of factors of interest; results were expressed as incidence rate ratios.

**Results of the review**

Fifty-seven RCTs with 21,472 patients in 312 trial arms were included in the review. Twenty-nine RCTs had losses to treatment of under 10%; randomisation was considered appropriate in 40 of the 41 trials describing it. Median follow-up post-treatment was 24 months (interquartile range 18 to 30 months).

Head-to-head comparisons found that failure rates were significantly higher in patients receiving only one to two months of rifampin than in those treated for three to four months (RD 0.3%, 95% CI 0.9 to 1.4; two RCTs), with no heterogeneity. Shorter durations of rifampin were associated with significantly higher rates of relapse compared with longer durations in all analyses. There was no difference between shorter and longer treatment durations for acquired drug resistance. Pooling of comparisons of intermittent schedules was not possible due to different schedule comparisons between trials.

Indirect comparisons confirmed the finding that rifampin durations of one to two months had higher failure and relapse rates than longer durations, and that rates of relapse were higher for shorter durations of rifampin, up to a treatment length of eight months. There were no significant differences between schedules using daily treatment, daily then thrice weekly, daily then twice weekly, or thrice weekly throughout treatment. Only one trial evaluated treatment twice weekly throughout therapy.

Meta-regression confirmed that one to two months of rifampin treatment resulted in higher incidence rates of failure, relapse and acquired drug resistance than longer durations. A number of other factors were found to have statistically significant relationships with treatment outcomes and full details were reported in the paper.

**Authors’ conclusions**

Treatment outcomes were significantly worse with shorter durations of rifampin or where there was initial drug resistance to isoniazid and/or streptomycin. Treatment outcomes were similar across the different intermittent schedules evaluated but there was insufficient evidence for administration twice weekly throughout treatment.

**CRD commentary**

The review question and the inclusion criteria were clear. Three relevant databases were searched, but the restriction of the review to published studies reported in three European languages may have led to the omission of relevant studies or increased the possibility of language and/or publication biases. The authors used methods designed to reduce reviewer bias and error in all stages of the review process.

The inclusion criteria included some requirements related to validity (bacteriological confirmation of eligibility and outcomes); other relevant criteria were appraised. The use of statistical pooling was reasonable. However, the authors also used indirect analysis methods, which are not as robust as direct head-to-head treatment comparisons. However, in this case it was undertaken primarily as a secondary analysis and the results accord with those of the conventional meta-analysis.

The authors’ conclusions reflected the results of the trials, which included a very large number of patients, and appear likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that there is evidence against the continued use of regimens that use rifampin only in the first two months of treatment; they are significantly and substantially inferior to regimens using rifampin for at least six months.
Research: The authors stated that there is a need for adequately powered clinical trials which assess dosing schedules, management of isoniazid resistance, and the optimal duration of treatment to prevent relapse.

Funding
Canadian Institutes of Health Research; Fonds de la Recherche en Sante du Quebec; World Health Organisation (WHO).

Bibliographic details

PubMedID
19753109

DOI
10.1371/journal.pmed.1000146

Original Paper URL
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000146

Other URL
http://ukpmc.ac.uk/abstract/MED/19753109

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibiotics, Antitubercular /administration & dosage /therapeutic use; Drug Administration Schedule; Drug Resistance, Bacterial; Humans; Isoniazid /therapeutic use; Randomized Controlled Trials as Topic; Recurrence; Regression Analysis; Rifampin /administration & dosage /therapeutic use; Risk Factors; Streptomycin /therapeutic use; Treatment Failure; Tuberculosis, Pulmonary /drug therapy

AccessionNumber
12009110008

Date bibliographic record published
14/04/2010

Date abstract record published
27/10/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.