Rifapentine vs rifampicin for the treatment of pulmonary tuberculosis: a systematic review

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CRD summary
The authors concluded that once weekly or less frequent use of rifapentine increases the risk of bacteriological relapse in HIV negative patients in comparison with twice or thrice weekly rifampicin. The authors' conclusion reflected the evidence presented, but given the small number of studies the conclusion should be interpreted with some caution.

Authors' objectives
To evaluate the effectiveness of rifapentine compared to rifampicin for the treatment of pulmonary tuberculosis.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), BIOSIS Previews, CBM and VIP database were searched for published studies. Wangfang database and ClinicalTrials.gov were searched for unpublished material. Searches were limited to studies in Chinese or English. Search terms were reported. References lists of relevant articles were searched.

Study selection
Randomised controlled trials (RCTs) that had patients with drug susceptible or previously untreated pulmonary tuberculosis confirmed by sputum smear and/or culture were eligible for inclusion in the review. Studies had to compare rifapentine directly with rifampicin. Concomitant anti-tuberculosis drugs needed to be the same in both study arms. Studies needed to report outcomes of cure (defined as a single negative *Mycobacterium tuberculosis* culture at the end of treatment or negative sputum smear two months after the cessation of treatment) and severe adverse events (defined as serious drug reactions that led to hospitalisation or discontinuation of treatment determined by the authors based on clinical signs or symptoms or laboratory examination). Additional outcomes of interest were bacteriological relapse rates.

Trials were conducted in either China or USA/Canada. Participants were aged 14 years or over. In most studies participants were human immunodeficiency virus (HIV) negative and rifapentine capsules were used. The dose and frequency of administration of rifapentine and rifampicin, and concomitant anti–tuberculosis drugs varied between studies.

Two reviewers independently selected studies for inclusion in the review. Any disagreements were resolved by discussion or the involvement of a third party.

Assessment of study quality
Study quality was assessed using criteria of randomisation, allocation concealment, blinding, reporting of loss to follow up/withdrawal and comparability at baseline. Each item was rated A, B or C to denote whether it was adequate, unclear or inadequate.

Studies with five grade A items were considered high-quality trials, studies with one or more B items and no C items were considered moderate quality and studies with one or more C items were considered low quality.

Two reviewers independently performed the study quality assessment. Any disagreements were resolved by discussion or by the involvement of a third party.

Data extraction
Data were extracted according to intention to treat using a predefined form in order to calculate relative risks (RR) and 95% confidence intervals (CI). Two reviewers independently performed the data extraction. Any disagreements were resolved by discussion or the involvement of a third party.
Methods of synthesis
Meta-analysis was performed on six subgroups of studies based on the frequency of administration of rifapentine and rifampicin (rifapentine twice weekly versus rifampicin daily; rifapentine twice weekly versus rifampicin twice weekly; rifapentine once weekly versus rifampicin daily; rifapentine once weekly versus rifampicin twice or thrice weekly; rifapentine twice tri-weekly or once fortnightly versus rifampicin twice or thrice weekly). Relative risks were combined in a fixed-effects model when statistical heterogeneity was absent (assessed with the $\chi^2$ test). A random-effects model was used when statistical heterogeneity was present and it was appropriate to combine trials. Additional subgroup analysis was performed according to treatment phase (whole course and continuation phase of treatment). Publication bias was assessed using the funnel plot.

Results of the review
Ten studies (n=3,218 patients) were included in the review. Sample size ranged from 40 to 1,004 patients. Nine studies were performed in HIV negative patients and one study was performed in HIV positive patients. Two studies were assessed as moderate quality and seven as low quality.

There was no statistically significant difference between rifapentine and rifampicin in terms of cure rates (nine RCTs), severe adverse events (eight RCTs), death (eight RCTs) or severe hepatotoxicity (six RCTs).

Bacteriological relapse rates were reported in nine trials, including one trial of HIV positive patients. Bacteriological relapse rates were only statistically significantly different for two subgroups: there was an increased risk of relapse when rifapentine was administered once weekly or less in comparison with rifampicin administered twice or thrice weekly (RR 1.71, 95% CI 1.13 to 2.58) and rifapentine administered twice tri-weekly or once fortnightly versus rifampicin administered twice or thrice weekly (RR 2.44, 95% CI 1.15 to 5.18).

For the one study of HIV positive patients, there was no significant difference between rifapentine and rifampicin in terms of sputum conversion rates, severe adverse effects or bacteriological relapse rates. However, four of the five relapse rates cases in the rifapentine group and none of the three relapse cases in the rifampicin group produced monoresistance to rifamycin. There was no evidence of publication bias.

Authors' conclusions
Once or twice weekly rifapentine and daily rifampicin had similar efficacy and safety for the treatment of HIV negative pulmonary tuberculosis; once weekly or less frequent use of rifapentine in comparison with twice or thrice weekly rifampicin increased the risk of bacteriological relapse. Rifapentine might increase the risk of resistance to rifamycin in HIV positive patients.

CRD commentary
This review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was comprehensive and included a search for both published and unpublished material. However, only studies in English and Chinese were eligible for inclusion in the review, which meant that the review may have been subject to language bias and relevant studies may have been missed. The study quality assessment tool was appropriate for the included study design. Synthesis methods were appropriate and took into account clinical heterogeneity in the form of different doses and dosing regimens. This was a generally well-conducted review with sufficient attempts to minimise reviewer error and bias. The authors' conclusion reflected the evidence presented, but given the small number of studies included in each meta-analysis the conclusion should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that rifapentine should be used with caution in HIV infected patients in view of the critical role of rifamycin in the fight against TB.

Research: The authors did not state any implications for research.

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