Rifampicin plus pyrazinamide versus isoniazid for treating latent tuberculosis infection: a meta-analysis


CRD summary
This well-conducted review compared the efficacy and safety of rifampicin plus pyrazinamide (RZ) with isoniazid for the treatment of latent tuberculosis infection in HIV-positive and HIV-negative individuals. The authors concluded that both regimens were effective and that mortality was equivalent. However, in HIV-negative patients, RZ groups experienced more adverse events. This conclusion should be treated with caution.

Authors' objectives
To evaluate the effectiveness and safety of rifampicin plus pyrazinamide (RZ) versus isoniazid (INH) for treating latent tuberculosis (TB) infection in individuals infected with the human immunodeficiency virus (HIV) and uninfected individuals.

Searching
MEDLINE (1996 to 2005), EMBASE (1984 to 2004), the Cochrane CENTRAL Register (Issue 4, 2005), BIOSIS Previews (1997 to week 50, 2005) the Chinese Biomedical Literature Database (up to April 2005) and the VIP Database (Chinese; 1989 to April 2005); the search terms were reported. The reference lists of retrieved articles were screened for further articles, while Wanfang (1995 to 2005) and ClinicalTrials.gov were searched for unpublished information. Only studies written in English or Chinese were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared 2 to 3 months' RZ therapy with standard INH therapy for 6 to 12 months were eligible for inclusion. The included studies all used varying regimens of the three drugs (further details were reported in the review).

Participants included in the review
Individuals with latent TB infection defined according to criteria of the American Thoracic Society and the Centers for Disease Control and Prevention were eligible for inclusion. Individuals with active TB or those with previously active TB were excluded from the review. Three studies (n=3,036) included HIV-infected patients and three (n=1,017) included non-HIV-infected individuals. Where reported, the mean age of the participants ranged from 30.5 to 59.7 years, and the mean length of follow-up from 1.5 to 3.1 years.

Outcomes assessed in the review
Eligible studies had to report the rate of TB development, death or serious adverse events. Active TB was diagnosed by culture or any other method defined by the study author; serious adverse events (e.g. severe hepatotoxicity) were defined as drug-related events resulting in treatment discontinuation as defined by the study author.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of each study. Any disagreements were resolved through discussion or by a third party.

Assessment of study quality
Two reviewers independently assessed the quality of the studies according to the methods and criteria used in the Cochrane Collaboration Handbook. The criteria employed were randomisation, allocation concealment, blinding, reporting of withdrawals and losses to follow-up, and baseline comparability. Any disagreements were resolved through discussion or by a third party.

**Data extraction**

Two reviewers independently extracted the data from each study. Any disagreements were resolved through discussion or by a third party. The data were extracted on an intention-to-treat basis and recorded as risk differences (RDs) with 95% confidence intervals (CIs). Authors were contacted by e-mail for missing data.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to the type of participants (HIV-infected versus uninfected). Where studies were combined, pooled RDs with 95% CIs were calculated for each outcome measure, using a fixed-effect model. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and the I-squared tests. Where present, potential sources of significant heterogeneity were explored using predefined subgroup analyses (trial quality, treatment duration, drug dosage etc.). Some clinical differences between the studies were evident from the data tables and review text.

**Results of the review**

Six studies, including five RCTs (n=3,464) and one quasi-RCT (n=589), were included in the review.

One trial was rated as high quality, four as low quality and one as moderate quality.

The funnel plots did not suggest evidence of publication bias.

The rates of TB infection were similar in both the RZ and INH groups, regardless of whether individuals were infected with HIV (3 studies; RD 0%, 95% CI: -1, 2) or not (3 studies; RD 0%, 95% CI: -2, 1). No significant heterogeneity was detected.

There was no significant difference in mortality between RZ and INH groups in both HIV-infected individuals (3 studies; RD -1%, 95% CI: -4, 2) and those not infected with HIV (3 studies; RD 0%, 95% CI: -1, 1). No significant heterogeneity was detected.

Severe hepatotoxicity.

Significant statistical heterogeneity due to differences in the duration of treatment was identified for both HIV-infected and uninfected individuals. Subgroup analyses suggested that this was due to differences in the duration of treatment (HIV-infected individuals) and the quality of the trials (non-HIV-infected individuals).

All serious adverse events.

There was significant heterogeneity in the studies of non-HIV-infected individuals, which subgroup analyses suggested was due to differences in study quality. Events were significantly more likely to occur in those treated with RZ in both the moderate quality study (RD 29%, 95% CI: 13, 46; 1 study) and low-quality studies (RD 7%, 95% CI: 4, 10; 2 studies) among non-HIV-infected individuals. Similarly significant heterogeneity was detected in the studies of HIV-infected individuals (3 studies), which subgroup analyses suggested was due to differences in the duration of treatment. However, for these individuals, events were significantly more likely in RZ-treated patients only in the trial where the duration of INH therapy was 12 months.
Authors’ conclusions
RZ was equivalent to INH with regard to efficacy and mortality, but the risks of severe adverse effects were greater with RZ than INH in non-HIV-infected individuals.

CRD commentary
This well-conducted review was based on a clear research question with clearly defined inclusion criteria. The authors searched a large number of electronic databases and other sources in order to locate both published and unpublished data. However, one study was excluded from the review as it was not written in Chinese or English. Each stage of the review process was carried out by two independent reviewers and quality was assessed using published methods.

Heterogeneity was assessed statistically and predefined subgroup analyses were used to investigate any potential differences in effects. In addition, studies differed in how they defined the incidence of TB and certain outcome measures; the authors acknowledged this as a limitation of the studies. Overall, given the heterogeneity between trials and the reliance on a limited number of small trials, some caution is advised when interpreting the findings of this review.

Implications of the review for practice and research
Practice: The authors stated that clinicians should be cautious about using RZ on account of its toxicity, especially in preventing TB in non-HIV-infected individuals.

Research: The authors stated that further large trials comparing RZ with INH are required.

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