Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis

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CRD summary
The authors concluded that later-generation fluoroquinolones may improve treatment outcomes for extensively drug-resistant tuberculosis even though drug-susceptibility testing demonstrated resistance to a representative fluoroquinolone. Incomplete reporting of review methods, limitations in the search, inability to isolate the effects of later-generation fluoroquinolone and evidence based on small observational studies mean that the findings should be interpreted with caution.

Authors' objectives
To evaluate outcomes for the treatment of extensively drug resistant (XDR) tuberculosis (TB) and identify factors associated with a favourable response.

Searching
PubMed and EMBASE were searched from inception to May 2009 for peer-reviewed reports. Search terms were reported. No language restrictions were applied. Biographies of retrieved articles were screened.

Study selection
Observational studies of patients with XDR TB confirmed by drug-susceptibility testing of *Mycobacterium tuberculosis* cultures were eligible if the treatment protocols included specified second-line drugs and sufficient data were provided to permit calculation of the proportion of patients with a favourable outcome. Studies were excluded if more than 50% of patients were still receiving treatment during the preparation of the report and no additional information was available or if less than three relevant cases were reported. In the review, favourable outcome was defined according to World Health Organisation criteria (WHO).

All studies reported that patients were treated under close supervision in hospital or ambulatory settings between 1984 and 2007 and all received at least 12 months of drug treatment after culture conversion. The mean number of drugs in XDR TB regimens ranged from 3.6 to 7.4. A later-generation fluoroquinolone was given to up to 92% of patients, linezolid was given to up to 100% of patients and 4% to 60% of patients underwent surgery. Most studies were conducted in South Korea, USA and Germany. Most studies did not include patients with HIV. Mean age of patients ranged from 31 to 48. Most studies defined cure using WHO criteria (details of other criteria used were reported).

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Proportions of patients with favourable outcomes and proportions of patients who died were extracted, and 95% confidence intervals (CI) were calculated.

Two reviewers independently extracted data and resolved disagreements with the help of a third reviewer. One author provided additional data.

Methods of synthesis
Pooled proportions of patients with outcomes of interest and 95% CIs were calculated using the DerSimonian and Laird random-effects model; pooled proportions were weighted by the inverse of the variance. Heterogeneity was assessed with the I² statistic. Sensitivity analysis was performed by exclusion of studies with potentially duplicate patients.
Univariate regression was used to examine the relationship of eight variables to favourable outcome (HIV prevalence, mean age, proportion of females, mean number of drugs in treatment regimen, mean number of likely active drugs in treatment regimen, percentage receiving later-generation fluoroquinolone, percentage receiving linezolid and percentage undergoing surgery).

Multivariate meta-regression was conducted using the two covariates shown to have a significant association with favourable outcome (age and fluoroquinolone use).

Subgroup analysis was used to compare studies in which at least 50% of patients received a later-generation fluoroquinolone with studies in which fewer than 50% of patients received this agent.

**Results of the review**
Thirteen retrospective observational studies were included (n=560 patients, range four to 158).

The weighted proportion of favourable outcomes was 43.7% (95% CI 32.8% to 54.5%; 13 studies). Significant statistical heterogeneity was found ($I^2=84\%$). Proportions ranged from 18% to 67%.

The weighted proportion of patients who died was 20.8% (95% CI 14.2% to 27.3%). Significant heterogeneity was found ($I^2=68\%$). Proportions ranged from zero to 50%.

Studies in which more than 50% patients were treated with a later-generation fluoroquinolone had a significantly higher proportion ($p=0.012$) of patients with favourable outcomes (59.3%, 95% CI 50.8% to 67.8%, $I^2=0\%$; five studies) than studies in which fewer than 50% received this agent (30.6%, 95% CI 17.7% to 43.5%, $I^2=74\%;$ five studies).

Studies in which patients were younger had a significantly higher proportion of patients ($p=0.019, 13$ studies) with favourable outcomes than studies with older patients. Other variables showed no significant association with favourable outcome in univariate analyses.

Age and the proportion of patients treated with a later-generation fluoroquinolone were highly correlated and so it was not possible to determine their individual effects in multivariate meta-regression.

**Authors' conclusions**
Use of later-generation fluoroquinolones may improve treatment outcomes for extensively drug resistant tuberculosis even though drug-susceptibility testing demonstrates resistance to a representative fluoroquinolone.

**CRD commentary**
The review question was clearly stated. Inclusion criteria were appropriately defined. No language restrictions were applied to the search. Limiting the search to published studies listed in two databases risked publication bias and may have resulted in omission of other relevant studies. Relevant information on the included studies was summarised. Study validity was not assessed and so results from these studies and any synthesis may not be reliable. Methods were used to minimise reviewer errors and bias in data extraction; it was unclear whether similar steps were taken in study selection. Studies were combined using meta-analysis, heterogeneity was assessed and the influence of various factors was examined. Heterogeneity among studies meant that summary estimates did not reflect the wide range of treatment outcomes in reported studies.

Incomplete reporting of review methods, limitations in the search, inability to isolate the effects of later-generation fluoroquinolone, small sample sizes and evidence based on less robust observational studies mean that the findings should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that the generalisability of the review findings was limited as the studies were conducted in high-income countries with a low to middle burden of TB.
Practice: The authors stated an urgent need for more research into the effect of later-generation fluoroquinolone for XDR TB. Information about interventions and outcomes for patients with XDR TB should be recorded systematically. Patients should be tested for resistance to later-generation fluoroquinolone.

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