Fixed-Dose Drug Combination for Treatment of Tuberculosis

JOSEPH L MATHEW

From the Advanced Pediatrics Centre, PGIMER, Chandigarh 160012, India.
jlmathew@rediffmail.com

Anti-tuberculosis therapy (ATT) with multiple antimicrobials, administered individually or as fixed dose combinations (FDC) is the key to control of tuberculosis. Arguments in favour of FDC include better patient compliance, simplification of prescriptions, easier management of drug supply, reduced programmatic cost, and less chances of developing drug resistance(1-3). WHO and other agencies also recommend FDC for delivering ATT(4).

However, the bioavailability of rifampicin in FDC may be reduced owing to chemical reaction with isoniazid in the acidic gastric environment; pyrazinamide and ethambutol catalyze this reaction(5,6). Using FDC with poor rifampicin bioavailability can make therapy inadequate and thereby potentially increase drug resistance. A multi-national study reported that poor rifampicin bioavailability was twice as common with FDC as compared to separate administration among various ATT preparations from different countries including India(7). Other arguments against FDC are: (*i*) younger children may receive slightly higher dose than required; (*ii*) development of side effects may necessitate omission/modification of the entire combination, and (*iii*) FDC may be more expensive than individual components in terms of cost per tablet.

For these reasons, although FDC are considered the international standard for tuberculosis treatment(4), the WHO cautions that only preparations with proven bioavailability should be used and publishes a list of prequalified products(8). Most of the FDC available in India are not listed therein. It is therefore relevant to examine the scientific evidence on FDC for treating tuberculosis in children.

RELEVANCE

FDC are liberally prescribed in children despite limited information on the pharmacological properties of most preparations marketed in India. The concerns highlighted above mandate that the value (or otherwise) of FDC in treating childhood tuberculosis be evaluated carefully.

The clinical question addressed in this systematic review of evidence is: "In people with tuberculosis (*population*), does antimicrobial administration through fixed-dose combinations (*intervention*) compared to separate administration (*comparison*) affect treatment effectiveness (*outcome*)?" Treatment effectiveness can be determined by clinical and/or microbiological cure, or surrogate outcomes such as antimicrobial pharmacodynamic/pharmacokinetic measurements. Other relevant outcomes include safety, emergence of antimicrobial resistance during therapy, compliance, patient satisfaction and cost.

CURRENT BEST EVIDENCE

A broad, sensitive Pubmed and Cochrane Library search with the terms "*(fixed-dose combination) tuberculosis*" was undertaken on 25 August 2009 without any filters/limits. This identified 65 relevant citations which were examined in detail for randomized controlled trials (RCT) addressing the clinical question. Five RCTs(9-13) evaluated

treatment efficacy, one examined relapse(14), two estimated the emergence of drug resistance(14,15), and two(16,17) examined bioequivalence of rifampicin in FDC versus separate administration. The five trials measuring efficacy also reported adverse effects of therapy (safety data).

Data from three RCTs(9,11,13) examining treatment efficacy in sputum smear-positive pulmonary tuberculosis could be pooled through meta-analysis. The pooled odds ratio for treatment failure with FDC is 0.70 (95% CI 0.39-1.25, I^2=10.6%, fixed-effect model, 1502 participants), suggesting that both FDC and separate administration have comparable efficacy (***Fig.* 1**). Two additional RCTs(10,12) among sputum positive pulmonary tuberculosis patients also reported comparable efficacy, but did not present data in a format that could be pooled. Only one RCT(14) was designed to evaluate long term efficacy of treatment by measuring relapse rate (smear or culture positivity), three to five years after treatment. The trial reported a non-statistically significant higher relapse rate with FDC (10.1% *vs.* 2.7%, *P*=0.07).

Two RCTs compared the emergence of antimicrobial resistance. One included over 5000 patients taking self-administered ATT either as FDC or separate administration(15). Antimicrobial resistance of isolates was measured twice, at least three months apart. Acquired drug resistance, defined as initial isolate sensitive and second isolate resistant, occurred in less than 0.5% patients; it was lower among those taking FDC (0.3%) compared to separate administration (1.0%). Another RCT(12) among 105 participants examined drug resistance in a small minority and reported that 4 patients developed resistance with FDC (all pyrazinamide) compared to 8 with separate administration (6 pyrazinamide, 2 ethambutol).

Two trials performed pharmacodynamic measurements to compare the bioavailability of rifampicin between FDC and separate administration. One was designed as an open, within-subjects, single-blind, cross-over study (each volunteer acting as own control) measuring multiple parameters such as peak drug concentration, time to achieve peak concentration, biological half-life of elimination and area under the curve (AUC)(16). All were comparable except peak concentration which was lower with FDC (but within the therapeutically acceptable range). Another randomized, cross-over comparison in healthy volunteers examined rifampicin bioavailability in FDC formulations available globally. Seven of ten FDC formulations were not bioequivalent to separate administration of rifampicin(17).

Three RCTs(10-12) reported lower frequency of various adverse effects with FDC, while two(9,13) reported comparable frequency. The data could not

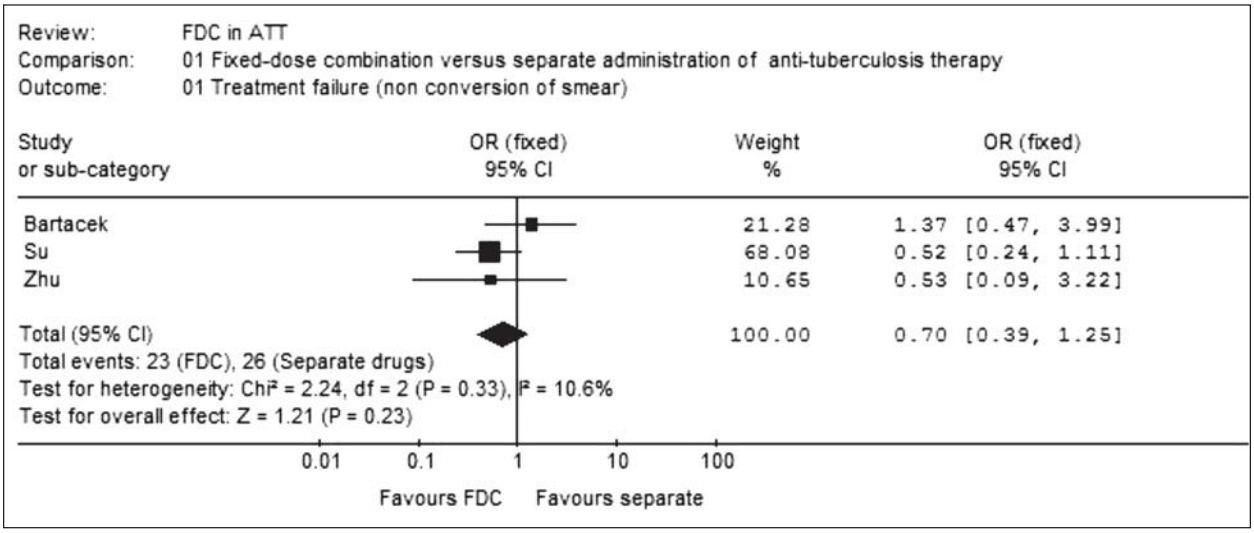

FIG. 1 *Treatment failure with fixed drug combination (FDC) vs. separate administration of anti-tuberculosis therapy (ATT).*

EURECA CONCLUSION IN THE INDIAN CONTEXT

- There is no evidence of superiority of fixed-dose combination ATT over separate administration in terms of treatment effectiveness.
- Marginal benefit in terms of compliance, convenience and lower acquired drug resistance may be offset by unpredictable pharmacological properties of many FDC preparations.
- The choice of FDC or separate administration of ATT should be individualized rather than empiric.

be pooled together. One trial(9) reported better patient acceptability with FDC and one trial(13) reported comparable treatment drop-out rate with FDC and separate administration. There was no RCT comparing therapy costs.

CRITICAL APPRAISAL

Most trials recruited only sputum smear positive cases, making the interpretation of results much more reliable and valid than assessment of treatment efficacy in suspected/latent tuberculosis. On the other hand, the results cannot be directly extrapolated to smear negative cases; this probably explains the complete absence of information in children. It is interesting that almost all the trials reported very high treatment success rate, which may not conform to the usual population pattern. This suggests better compliance to therapy during the course of clinical trials (the Hawthorne effect) and not necessarily treatment efficacy alone.

It is important to note that current best evidence does not support the presumed superiority of FDC over separate administration. This may be because either such superiority does not exist or due to low treatment failure rate in the available trials (limited scope for improvement). If the former presumption is correct, then trials need to be designed to prove non-inferiority, which is somewhat different from the usual RCT design. Either way, it suggests that the benefits of FDC (if any) relate to operational issues (drug procurement, storage, transport) and convenience (slightly better compliance) rather than clinical benefit. Given these considerations, a blanket recommendation favouring FDC ATT is difficult to appreciate.

EXTENDIBILITY

Many of the included trials were conducted in developing countries with population characteristics, disease prevalence, treatment protocols, compliance rates etc similar to India. Hence the evidence is applicable even though none of the trials was conducted here. It is not clear whether the available data can be extended to children and paucibacillary/smear-negative cases.

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