Shortening tuberculosis treatment: lessons from fluoroquinolone trials

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In clinical trial settings the standard 6-month regimen for drug-sensitive pulmonary tuberculosis (TB) can achieve relapse-free cure in >95% of people. However, poor adherence may increase the risk of relapse and lead to acquired drug resistance. Shortening TB treatment duration has become a major priority for the global TB control programme with potential patient benefits and reduction of selection pressures that lead to spread of new drug-resistant strains.(1)

Attempts to use shorter courses of standard regimen drugs have not been successful except in smear negative disease;(2, 3) and recent research has focused on fluoroquinolones, currently used within regimens for drug-resistant TB. A Cochrane review of five studies evaluating fluoroquinolone-containing six month regimens to treat drug sensitive disease concluded that the available evidence was of low quality, with the only consistently reported clinical outcome being all-cause mortality.(4) However, data from mouse models and phase 2 trials suggested use of fluoroquinolones may permit shortening of treatment for drug sensitive-TB from six to four months.(5) This has now been evaluated in humans through four large phase 3 randomised controlled trials. Despite fluoroquinolone-containing regimens leading to greater culture negativity rates at 2 months, this did not translate into improved clinical outcomes when treatment was shortened.

The RIFAQUIN,(6) OFLOTUB(7) and REMoxTB(8) trials have benefitted from larger patient numbers, over 18 months follow-up and robust methodology (such as the ability to differentiate relapse from reinfection due to strain typing). A trial run by the Indian National Institute for Research in Tuberculosis (NIRT) was discontinued early on account of unacceptable relapse rates (Figure 1).(9) The non-inferior result of the RIFAQUIN 6-month arm in which high dose rifapentine and moxifloxacin were given once weekly in the continuation phase appears consistent with findings from previous 6-month trials of fluoroquinolones suggesting that they are broadly equivalent to the standard regimen.

Apart from the RIFAQUN 6-month once-weekly regimen which could be useful in certain settings, it is clearly disappointing that despite these large trials, which have each cost several million dollars and lasted up to 10 years, we still remain with the same 1970s 6-month regimen. As fluoroquinolones alone do not seem to allow treatment shortening, it is important to determine which other of the new drugs currently in development might be successful and how the process of evaluation in clinical trials can be sped up.

Stratified treatment

Ideally a treatment regimen would be given to all patients but this may mean that the majority of cases receive unnecessarily prolonged treatment. An alternative approach would be to revisit stratification of cases to select those who may be suitable for shortened therapy. A four month regimen using rifampicin, isoniazid, pyrazinamide and ethambutol was shown to be effective treatment for smear negative disease in Hong Kong in the 1980s.(3) The majority of recent trials have focused exclusively on sputum smear positive disease. With the advent of molecular diagnostics, and the scaling up of active case finding, it may now be possible to define a group of patients who might benefit from shortened therapy.

Other simple markers of severity could include smoking, HIV infection and chest radiographic cavitation. Shortening treatment in patients with cavitation who also had negative cultures after 8 weeks has been shown to be associated with higher relapse rates, although the modest increase may be acceptable for a shorter regimen.(2, 10, 11) Stratified analysis of data from the recent 4-month fluoroquinolone trials may provide further evidence to support this hypothesis. Stratification could also be made possible through development of an effective biomarker for disease burden and/or response to treatment such as the semi quantitative outputs from GeneXpert or the Molecular Bacterial Load (MBL) assay, levels of which have been shown to be associated with relapse probability and changes in bacilliary load on liquid and solid culture over the first 14 days of treatment.(12)

The role of multi-arm multi-stage trials

Previous attempts to investigate new treatment combinations involved initial animal work and early phase human studies before progressing to large randomised controlled trials of one or two regimens. The new results discussed above demonstrate that: (1) the present mouse model of human TB does not fully represent the course of human infection and (2) 8-week culture conversion is not a completely reliable marker of the later course of human infection, potentially due to bacterial persisters. Using such models may inadvertently mean that effective agents are screened out, thereby increasing the chances of failed phase III trials.

A potential solution may be to accelerate clinical trials including safety analyses of new drugs and assessment of combinations in human trials to evaluate efficacy as soon as possible. The multi-arm multi-stage (MAMS) design identifies the best regimen through parallel evaluation of a number of different regimens, with sequential interim analyses designed to stop recruitment to arms unlikely to be sufficiently effective.(13) Examples of currently ongoing and planned trials evaluating new drugs include PanACEA MAMS-TB (ClinicalTrials.gov NCT01785186), and TRUNCATE-TB. PanACEA MAMS-TB is a phase IIb study evaluating combinations of high-dose rifampicin, moxifloxacin, and the new drug SQ109 for DS-TB in four trial arms. This approach has allowed two arms with SQ109 to be dropped after the first interim analysis. The TRUNCATE-TB phase II/III trial with a MAMS design plans to evaluate a number of novel combination regimens with recruitment starting in 2015. Even where a classical MAMS design is not possible, multiple arms as currently planned for the STREAM trial, evaluating shorter multidrug resistant TB regimens including higher doses of moxifloxacin, would increase efficiency.

Given the disappointing results of the recent 4-month fluoroquinolone trials, it is imperative that the lessons learnt are combined with the well-established clinical trial infrastructure built up to accelerate the next phase of efforts to improve TB treatment. Novel approaches to trial design, use of recently developed drugs and revisiting patient stratification may lead to shorter TB therapy.

Figure

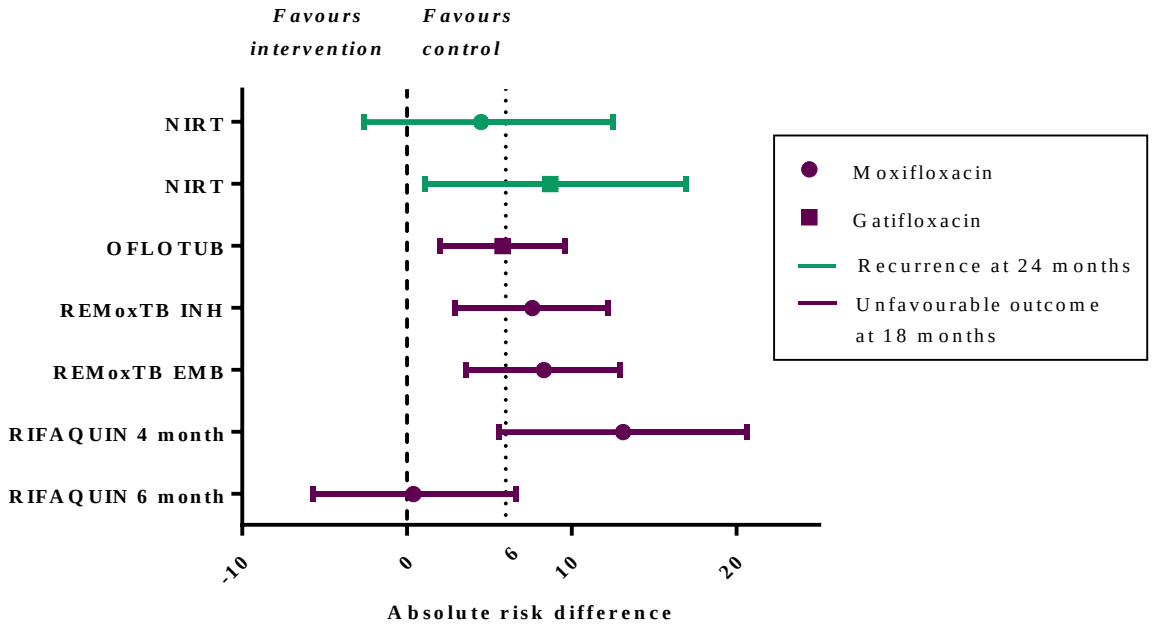

Figure legend: Effect of quinolone-containing regimens compared to standard treatment assessed by modified intention-to-treat analysis. Unfavourable outcome at 18 months post-randomisation follows trial-specific definitions which were broadly similar (include treatment failure and relapse). Unfavourable outcome at 18 months was not the primary endpoint for OFLOTUB but plotted here for comparison with RIFAQUIN and REMoxTB. Outcome for NIRT study was recurrence of TB 24 months post-randomisation in those with a favourable response at the end of treatment. All trials used a 6% margin of non-inferiority (dotted line) apart from the NIRT study which used a 5% margin. 95% confidence intervals are shown. High-dose rifapentine was given with moxifloxacin in the continuation phase in the RIFAQUIN study. REMoxTB EMB = isoniazid replaced with moxifloxacin, REMoxTB INH = ethambutol replaced with moxifloxacin.

References

1. WHO. Priorities for tuberculosis research. 2013.
2. Johnson JL, Hadad DJ, Dietze R, Maciel EL, Sewali B, Gitta P, et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. Am J Respir Crit Care Med. 2009;180(6):558-63.
3. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1989;139(4):871-6.
4. Ziganshina LE, Titarenko AF, Davies GR. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive). Cochrane Database Syst Rev. 2013;6:CD004795.
5. Lounis N, Bentoucha A, Truffot-Pernot C, Ji B, O'Brien RJ, Vernon A, et al. Effectiveness of once-weekly rifapentine and moxifloxacin regimens against Mycobacterium tuberculosis in mice. Antimicrob Agents Chemother. 2001;45(12):3482-6.
6. Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med. 2014;371(17):1599-608.
7. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588-98.
8. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577-87.
9. Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One. 2013;8(7):e67030.
10. Phillips PP, Nunn AJ, Paton NI. Is a 4-month regimen adequate to cure patients with non-cavitary tuberculosis and negative cultures at 2 months? Int J Tuberc Lung Dis. 2013;17(6):807-9.
11. Chang KC, Sterling TR, Yew WW. Are we ready to shorten the treatment duration for non-cavitary pulmonary tuberculosis? Int J Tuberc Lung Dis. 2013;17(6):712.
12. Honeyborne I, Mtafya B, Phillips PP, Hoelscher M, Ntinginya EN, Kohlenberg A, et al. The molecular bacterial load assay replaces solid culture for measuring early bactericidal response to antituberculosis treatment. J Clin Microbiol. 2014;52(8):3064-7.
13. Phillips PP, Gillespie SH, Boeree M, Heinrich N, Aarnoutse R, McHugh T, et al. Innovative trial designs are practical solutions for improving the treatment of tuberculosis. J Infect Dis. 2012;205 Suppl 2:S250-7.

Authors' contributions

IA proposed the concept, which was further developed by CN, ML, PP, AN, TM. CN produced the first draft with input from ML and IA. All authors critically reviewed the comment and have seen and approved the final version.

Conflict of interest statements

No conflicts of interest to declare

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