Can we shorten or simplify tuberculosis treatment?

The challenges of treating tuberculosis

Tuberculosis (TB) is a major global health problem. In 2012 there were 8.6 million new cases of TB, and 1.3 million deaths. Effective treatment options are available for treating TB, with treatment being successful in 87% globally and 79% of African new TB cases treated in 2011.

However, the standard WHO-recommended regimen (2 months of daily ethambutol, isoniazid, rifampicin and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)) involves taking the drugs daily for 6 months. This can make adherence to treatment hard, and has substantial costs to the health system and patients.

Shortening the length of time treatment needs to be taken for, or reducing the frequency at which the doses need to be taken, may help to reduce the burden on health systems, the costs of treatment, and make treatment easier for patients. Reducing the number of treatment doses might also reduce toxicity and improve adherence. If the length of treatment could be reduced it may help to increase the proportion of patients who complete their treatment, and reduce the risk of emergence of multi-drug resistance.

Addressing these challenges – the RIFAQUIN trial

Developing shorter treatment regimens, or ones that need less frequent doses, are priorities for TB research. These regimens would need to be as effective as the current 6 month daily regimen. If these regimens involve higher doses than currently used, trials would need to demonstrate that it does not lead to unacceptable levels of side-effects. Drug resistance is another area of concern that needs to be considered alongside efficacy and safety information from trials.

The RIFAQUIN trial was a randomised controlled trial comparing two new regimens against the standard 6 month daily dosing regimen for new smear-positive pulmonary tuberculosis. It was carried out in South Africa, Zimbabwe, Botswana, and Zambia, and involved 827 participants, of whom 233 were HIV positive. Participants were followed up for 12 to 18 months.

The regimens used in the trial were:

- 6 month standard daily regimen: 2 months of daily ethambutol, isoniazid, rifampicin and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)
- 4 month regimen: 2 months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P)
- 6 month weekly continuation regimen: 2 months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P)

Participants were given a meal of two hard-boiled eggs and bread before each dose of rifapentine to improve absorption of the drug. Previous trials giving 600mg rifapentine once weekly had unacceptable relapse rates and there was concern about HIV-infected patients who relapsed acquiring rifampicin resistance. In RIFAQUIN the dose of rifapentine was increased in order to assess whether the number of relapses could be reduced and to prevent the acquisition of rifampicin resistance. RIFAQUIN used

Key points

- Current standard treatment regimens for new smear-positive pulmonary TB are effective, but require treatment for 6 months, with daily dosing – this puts a big burden on patients and the health system
- A six month regimen of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide for 2 months followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P) is as effective as the standard 6-month daily regimen (2EHRZ/4HR)
- A four-month regimen of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide for 2 months followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P) is not as effective as the standard 6-month regimen (2EHRZ/4HR)
- Reducing dose frequency to once a week during the continuation phase may help to reduce the burden on the health system and patients, but further research is needed on acceptability, adherence and cost-effectiveness
moxifloxacin rather than isoniazid in the study regimens as it has a long half-life and greater bactericidal activity against dormant bacilli than isoniazid.

Was the once-weekly continuation regimen effective?

RIFAQUIN found that the once-weekly continuation phase regimen was as good as the standard daily regimen. It was also safe and well tolerated. This is the first regimen with continuation phase dosing of less than 3 times per week to be found to be as good as the standard regimen. There was no acquired drug resistance among participants on the once-weekly regimen.

Was the shorter regimen effective?

Disappointingly, RIFAQUIN found that the shorter regimen was not as good as the standard 6 month daily regimen, with 14% more participants having unfavourable outcomes. The continuation phase of twice weekly 900mg rifapentine with moxifloxacin was inadequate to shorten treatment. Despite the disappointing results, the regimen was safe and well tolerated. There was no acquired drug resistance among participants on the 4-month regimen.

Two other trials investigating 4-month regimens containing fluoroquinolones (the REMoxTB and OFLUTUB trials) have recently published results. Both these trials found, like RIFAQUIN, that the shorter regimens were not as effective as the current standard 6-month regimen.

What are the implications of these results?

Finding that the once-weekly continuation phase regimen was as good as the standard regimen is good news. However, it does not mean that all TB treatment programmes should automatically switch over to this regimen. There are several important context-specific factors that need to be taken into account in this decision:

- What are the costs of the new regimen to both the health system and patients? This will depend on the relative costs of the drugs, how therapy is currently observed (do patients have to travel to a health facility daily, or is observation carried out by a family member in the home) how it would be observed if the once-daily regimen was adopted, and the travel and time costs associated with these approaches.

  - How would this affect the workload of health-workers?
  - Is the once-weekly regimen acceptable to both patients and health-workers?
  - How will it affect adherence to treatment? Will once weekly dosing improve adherence, or does the routine of taking drugs every day help patients adhere?
  - How common is isoniazid resistance? The new regimen does not contain isoniazid, therefore it is particularly attractive in areas where isoniazid resistance is high.
  - Are there any patient groups who would particularly benefit from once-weekly supervision? This is much simpler for both the patient and the health service.

Research needs

While RIFAQUIN provides information about efficacy, safety and drug resistance associated with the once-weekly continuation phase regimen, a number of important questions remain. Research is urgently needed on:

- Costs and cost-effectiveness
- Acceptability and adherence
- Pharmacokinetics of high doses of rifapentine with efavirenz

References


Credits

This briefing document is an output from the RIFAQUIN trial, which was carried out by Inter TB. It was written by Annabelle South, Karen Sanders, Patrick Phillips, Andrew Nunn and Amina Jindani on behalf of the RIFAQUIN trial team. The RIFAQUIN trial was funded by EDCTP.