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Treating latent tuberculosis with rifampin: is it the cheaper option?

Jason E Stout, David P Holland

Treatment of latent tuberculosis infection (LTBI) is an important measure for tuberculosis control in the developed world. A recent study estimated that between 291 000 and 433 000 persons started LTBI treatment in the USA in 2002 and that between 4000 and 11 000 cases of active tuberculosis were prevented by this treatment.[1] However, many persons for whom LTBI treatment is recommended fail to initiate or complete treatment. Another recent cross-sectional survey of clinics in the USA and Canada showed that fewer than 50% of persons prescribed LTBI treatment completed the prescribed course.[2] Key barriers to successful completion of treatment include the length and suboptimal tolerability of the 9-month course of isoniazid that is most frequently used for LTBI treatment. Shorter better-tolerated regimens are clearly needed.

The study by Aspler *et al*[3] in this issue of *Thorax* (***see page 582***) examines one such regimen—namely, 4 months of daily rifampin. This regimen, while recommended as an alternative option for LTBI treatment by the Centers for Disease Control and Prevention,[4] has not been widely adopted in the USA. Major barriers to adoption include the possibility of inadvertent treatment of active tuberculosis with rifampin resulting in rifampin-monoresistant disease, concerns about effectiveness and the increased cost of rifampin compared with isoniazid. Aspler *et al* addressed the latter concern by prospectively examining health system costs in a randomised trial comparing 9 months of daily isoniazid with 4 months of daily rifampin for LTBI treatment. The study was conducted in centres in Canada, Brazil and Saudi Arabia, so health system costs in both high- and middle-income settings could be evaluated. Costs were all converted to 2007 Canadian dollars. The primary trial was designed to assess safety and tolerability, so the efficacy of rifampin was assumed to be equivalent to isoniazid in the base case scenario and varied widely. The average per patient cost for the isoniazid arm (N=427) was $C970 compared with $C854 for the rifampin arm (N=420), a statistically significant difference in favour of rifampin ($p<0.0001$). The difference in cost between the two regimens was primarily driven by the greater number of clinical visits required for the 9-month isoniazid regimen (average cost $C692 per patient for scheduled clinical visits vs $C481 for rifampin). Toxicity was a secondary driver of the cost differential, with $C113 per patient spent on non-scheduled care (ie, assessment or management of potential toxicity) in the isoniazid group and $C79 per patient in the rifampin group ($p=0.008$). Using these cost data, the authors deemed the rifampin regimen to be cost-saving while preventing more tuberculosis cases if the efficacy of the regimen in preventing tuberculosis reactivation was 75% or greater (assuming 9 months of isoniazid is 90% efficacious). This finding held when both Brazilian and Canadian health system costs were used, and over a range of assumptions regarding drug costs.

A growing body of evidence suggests that 4 months of daily rifampin may be an attractive regimen for the treatment of LTBI. A recent meta-analysis examined data from four studies (3336 subjects) and concluded that 4 months of treatment with rifampin was associated with about half the non-completion rate of 9 months of isoniazid treatment and 12% the risk of hepatotoxicity.[5] This meta-analysis estimated a cost saving of US$213 per patient by using rifampin instead of isoniazid for LTBI treatment, a value similar to the findings of Aspler *et al.* Similarly, another recently published decision analysis concluded that 4 months of rifampin treatment was cost-saving compared with 9 months of isoniazid, assuming that rifampin is no worse than 17% less efficacious than isoniazid.[6] However, cost determinations are certainly affected by local costs and monitoring practices; a retrospective cohort analysis from a public health clinic in Massachusetts found that, given local drug and provider visit costs, the treatment costs for 9 months of isoniazid were less than those for 4 months of rifampin.[7]

Of course, while treatment costs are certainly important, the overall cost-effectiveness of LTBI treatment is heavily influenced by the overall effectiveness of a given regimen in prevention of active tuberculosis. If 4 months of rifampin treatment prevented many more cases of active tuberculosis (due to higher

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completion rates), it could potentially be cost-effective or even cost-saving in the long run despite higher short-term treatment costs. Unfortunately, such benefits are difficult to estimate at the present time given the uncertainties surrounding the efficacy of rifampin. Aspler *et al* address this issue by assuming that 4 months of treatment with rifampin reduced the risk of active disease by at least 60%, approximately the same as 3 months of rifampin. While this minimum value seems reasonable, the requirement for wide variations in their estimate underscores the need for additional data on rifampin monotherapy.

While unknown efficacy has been an issue, the major concern about use of rifampin for LTBI treatment has been the possibility of inadvertent treatment of active tuberculosis with rifampin monotherapy which would lead to acquired rifampin monoresistance. Rifampin is a vital drug for tuberculosis treatment and, while patients infected with isoniazid-monoresistant isolates can often be successfully treated with 6 months of therapy, patients infected with rifampin-monoresistant isolates usually require 12–18 months of treatment. To date, there has been a single case report of rifampin resistance apparently developing de novo on treatment for LTBI.[8] Non-adherence and poor absorption (due to vomiting) probably played a role in this case and no further cases have been reported in subsequent trials, so the real risk of rifampin resistance developing on therapy may be quite small. Nonetheless, thorough standardised evaluation for active tuberculosis prior to initiation of LTBI treatment and close observation while on treatment will be an essential component of any tuberculosis control programme that initiates large-scale rollout of the 4-month rifampin regimen. Any potential cost savings of this regimen would be quickly offset by the cost of the lengthy treatment for rifampin-monoresistant disease. Furthermore, the pharmacokinetic interactions between rifampin and a number of other medications (which generally are not a significant issue with isoniazid) also pose a challenge to wide-scale implementation of this regimen. In particular, the use of rifampin for LTBI treatment will be limited in patients infected with HIV due to significant drug–drug interactions between rifampin and several classes of antiretroviral drugs.[9]

Regardless of these concerns, shorter better-tolerated regimens with higher completion rates in high-risk populations are needed to make progress towards tuberculosis elimination in the developed world. Given funding constraints for tuberculosis control, the cost-effectiveness of these regimens is of paramount importance to make them viable for public health practice. The study by Aspler *et al* is an important addition to the evidence that the 4-month rifampin regimen may be a less expensive and more effective tool in the fight against tuberculosis. We look forward to a conclusive demonstration of the effectiveness of the regimen in the authors' ongoing clinical trial.

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Better lungs for better legs: novel bronchodilator effects in COPD

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Limitation of exercise capacity plays a central role in the life of the patient with chronic obstructive pulmonary disease (COPD), both as a marker of well-being[1] and as an indicator of a poor prognosis.[2] Our ability to characterise this crucial aspect of disease has grown rapidly in the last decade and with this so has our understanding of the many complex reasons for exercise impairment. It has long been recognised that the maximum ventilation during exercise is related to the initial FEV_1 (forced expiratory volume in 1 s), with several formulae being developed to predict this. It was accepted that an inability to sustain a high level of ventilation would limit exercise performance in COPD, although exactly why this happened was uncertain. In the last decade there has been compelling evidence that changes in the operating lung volumes during exercise lead to mechanical limitation of inspiration and hence of tidal volume, which is associated with the sensation of breathlessness.[3 4] Dynamic hyperinflation is a very consistent finding in COPD and can even occur early in the natural history of COPD, at least in symptomatic people.[5] However, not all patients are limited exclusively by breathlessness on exertion, and data from the McMaster group in the 1990s pointed out that many patients were limited by a feeling of heaviness or fatigue in their legs, either along with breathlessness or dominating this sensation.[6] As a result, attention

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