Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Rifampin (RIF) was compared with isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI). RIF (10 mg/kg, up to 600 mg) was administered daily for 4 months, whereas INH (5 mg/kg, up to 300 mg) was administrated daily for 9 months.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older, with documented tuberculin skin tests that met the criteria for a positive test by Canadian standards (Long R, 2000, see 'Other Publications of Related Interest' below for bibliographic details), and with 9INH as the initial recommended treatment for LTBI. Contacts of INH-resistant cases and patients with hypersensitivity to RIF were excluded. Also excluded were those who were taking therapy with potential interactions with RIF, without any acceptable alternative being available, or who refused such alternatives.

Setting
The setting was secondary care. The economic study was carried out in Quebec, Canada.

Dates to which data relate
The effectiveness and resource use data were gathered from patients who were enrolled in the study from January to October 2002. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
It was calculated that the randomisation of 58 patients per arm provided 80% power to detect significantly better treatment completion with 4RIF (alpha 0.05, one-sided test), expecting 70% completion with 9INH and 90% with 4RIF. All eligible patients (n=227) who were recommended to take 9INH for LTBI between January and October 2002.
were referred to the study for screening. Of the patients screened, 18 were not eligible and 93 refused to participate. Of the refusals, 37 patients preferred standard therapy, 38 patients did not want research, 5 patients preferred RIF, 1 patient was unwilling to change contraception and 12 patients did not give a reason. Thus, a total of 116 patients accepted to participate and were randomised to either the 9INH group (n=58) or the 4RIF group (n=58).

Study design
This was an open-label randomised controlled trial that was conducted in a single centre, a university-affiliated respiratory hospital in Canada. Randomisation was stratified by risk of TB using an internet-accessible computerised program. The length of follow-up seems to have been 9 months in the 9INH group and 4 months in the 4RIF group. One patient initially allocated to the 4RIF group refused to start treatment. Non-blinded assessments were carried out.

Analysis of effectiveness
The effectiveness analysis was conducted on an intention to treat basis. The primary outcome was the percentage of prescribed doses taken, as measured by an electronic device in the cap of the pill container. The patients were considered to have completed therapy if they took more than 80% of the total prescribed doses within 20 weeks for 4RIF, or 43 weeks for 9INH. The secondary outcomes included adverse events resulting in permanent discontinuation of therapy. Drug-induced hepatitis was defined as liver transaminase levels more than three times the upper limits of normal with symptoms, or transaminase levels more than five times the upper limits of normal without symptoms. The characteristics of those patients who refused and of the patients randomised to the two treatment arms were not significantly different. The characteristics of the participants in the 4RIF and 9INH groups were similar.

Effectiveness results
Of the 58 patients randomised to the 4RIF group, 53 (91%) completed therapy and 50 (86%) took more than 90% of doses. In the 9INH group, 44 (76%) completed therapy and 36 (62%) took more than 90% of doses. Both differences were significant, (p<0.05).

The proportion of doses taken each month was generally higher with RIF, although it was significantly higher only in month 2 (96.8% versus 90.8%; p=0.03).

Major adverse events, which resulted in permanent discontinuation of therapy by their treating physician, occurred in 8 (14%) patients in the 9INH group and 2 (3%) patients in the 4RIF group (relative risk 0.25, 95% confidence interval: 0.1 - 1.1). Three (5%) patients in the 9INH group suffered drug-induced hepatitis versus 0 patients in the 4RIF group.

Minor symptoms, which did not result in any change of therapy, were generally similar for the two regimens. The exception was a significantly greater occurrence of fatigue with RIF (15% versus 4%; p<0.001).

Clinical conclusions
Significantly more patients in the 4RIF group completed an adequate course of therapy, with less frequent major adverse events, compared with the 9INH group.

Measure of benefits used in the economic analysis
No summary measure of health benefits was used in the economic evaluation. The study was, in effect, a cost-consequences analysis.

Direct costs
Discounting was not relevant given the time horizon of the analysis. The direct costs considered in the economic analysis seem to have been those of the hospital. They included clinical visits (routine and unscheduled visits), emergency room, consultations (gastrointestinal and dermatology), drug costs, pharmacist fees, additional chest X-ray, and laboratory tests (liver function tests, sequential multiple analyser-seven, and hepatitis serology). The costs for the
electronic monitors to test the number of prescribed doses taken were not included. The unit costs and the quantities of resource used were reported separately. The institutional costs were based on actual costs and the Medical Chest Institute in 2003. Professional fees were gathered from the 2003 reimbursement schedule of the Regie de l’Assurance Maladie du Quebec. The medication costs were based on pills dispensed, pharmacist fees and global TB drug facility prices. The total costs and the mean costs per patient allocated and per patient completed were reported.

**Statistical analysis of costs**  
The costs were treated deterministically.

**Indirect Costs**  
The indirect costs were not included in the analyses.

**Currency**  
Canadian dollars (Can$). The exchange rate was Can$1 = US$0.75 at January 2004.

**Sensitivity analysis**  
Sensitivity analyses were not conducted.

**Estimated benefits used in the economic analysis**  
See the 'Effectiveness Results' section.

**Cost results**  
The total costs of follow-up were Can$27,014 in the 9INH group and Can$17,182 in the 4RIF group.

The mean cost per patient allocated was Can$466 in the 9INH group and Can$296 in the 4RIF group.

The mean cost per patient completed was Can$614 in the 9INH group and Can$324 in the 4RIF group.

The total costs of non routine care were Can$1,819 in the 9INH group and Can$739 in the 4RIF group. The mean cost per patient allocated was Can$31 in the 9INH group and Can$13 in the 4RIF group.

**Synthesis of costs and benefits**  
Not relevant, as a cost-consequences analysis was performed.

**Authors' conclusions**  
Significantly more patients treated with 4 months' rifampin (4RIF) completed their therapy, with significantly lower follow-up costs and somewhat less frequent major adverse events, compared with 9 months' isoniazid (9INH). The authors argued that this small trial did not have adequate power to assess safety or efficacy. Therefore, they emphasised that these results should not be interpreted to mean that 4RIF can replace 9INH for routine treatment of latent tuberculosis infection (LTBI).

**CRD COMMENTARY - Selection of comparators**  
The authors clearly stated the rationale for their choice of the comparator. The current recommended standard therapy at the time of the study was 9INH. You should decide whether it represents a valid comparator in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness evidence came from an open-label randomised controlled trial, which was appropriate for the study question. The main strengths of the study were that power calculations were performed, the methods used for sample selection and randomisation were given, and the baseline comparability of the groups was stated. In addition, the numbers of patients who refused or were excluded from the initial sample were clearly reported. However, the authors reported some limitations of their study. First, the trial did not have adequate power to assess safety and efficacy. Second, the absence of blinding might have introduced bias into the outcome assessment.

Validity of estimate of measure of benefit
Not relevant since a cost-consequences analysis was performed.

Validity of estimate of costs
It appears that all the costs relevant to the perspective adopted in the study have been included. The price year and the unit costs were reported, thereby facilitating reflation exercises in other settings. The unit costs and the quantities of resource used were reported separately, thus enhancing the reproducibility of the study in other settings. Resource use was taken from this single study and a statistical comparison of quantities between the two treatments was performed. The cost estimates would appear to be specific to the study setting. Since all the costs were incurred during less than two years, discounting was appropriately not performed.

Other issues
The authors compared their effectiveness findings with those of other trials, showing a similar completion rate for 9INH and lower incidence rates of adverse events. The authors suggested that this might have reflected the selection of persons at lower risk for adverse events into the trial. The authors partially addressed the issue of generalisability. They argued that the process of routine care was disrupted as little as possible and that all patients, except those in whom RIF was clearly contraindicated, were included in the study. Therefore, the study results should be realistic and relevant to routine practice. Sensitivity analyses were not performed. The authors stressed that patient compliance may have been overestimated if patient behaviour was influenced by the knowledge that every opening of the pill container was recorded electronically.

Implications of the study
The authors suggested that the next step is a trial with adequate power to assess safety and tolerability in a group of patients who are representative of those likely to receive this therapy in future. A careful assessment of the safety of the 4RIF regimen is needed before undertaking an efficacy study. If the safety and tolerability of 4RIF are equivalent to, or better than those of 9INH, then a large-scale efficacy study would be justified.

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