Preventing Mycobacterium avium complex in patients who are using protease inhibitors: a cost-effectiveness analysis
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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
Five strategies were compared for the prevention of Mycobacterium avium complex (MAC) in patients with human immunodeficiency virus (HIV) disease, who were receiving protease inhibitors. The strategies evaluated were:

- no prophylaxis;
- azithromycin, 1,200 mg once weekly;
- clarithromycin, 500 mg twice daily;
- rifabutin, 150 mg once daily; and
- azithromycin (1,200 mg weekly) combined with rifabutin (150 mg once daily).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of men aged 35 years, suffering from advanced HIV disease, who were receiving protease inhibitors and Pneumocystis carinii prophylaxis.

Setting
The setting was the community. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and resource use data were derived from studies published between 1991 and 1998. The price year was 1997.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies.

Modelling
A Markov model was used to simulate the natural history of late stage HIV disease. The base-case was a hypothetical 35-year-old man with symptomatic HIV disease receiving protease inhibitors, who entered the model when his CD4
count reached a level of 100E6 cells/L. At the end of each 1-month cycle, if the patient had survived, the transition probabilities for the occurrence of a side-effect and the development of a new AIDS-defining illness (ADI) were estimated. A new ADI was classified as either minor, major or MAC.

**Outcomes assessed in the review**
Numerous outcomes were assessed in the review and used as input parameters in the model. Only the following outcomes are reported in this abstract:

- the annual probability of dying,
- the annual probability of developing a new ADI,
- the relative hazard of developing either MAC or severe side-effects with the four drug therapies,
- the annual probability of developing a new ADI, and
- the rate of CD4 decline.

**Study designs and other criteria for inclusion in the review**
Different study designs were included in the review. In particular, the effectiveness of the MAC prophylaxis was based on randomised trials.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
The effectiveness evidence was derived from a review of 24 primary studies.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The annual probability of dying was 4%.

The annual probability of developing a new ADI was 13%.

The relative hazard of developing MAC was 0.45 with rifabutin, 0.34 with azithromycin, 0.31 with clarithromycin, and 0.13 with the azithromycin-rifabutin combination.
The probability of severe side-effects was 0.16 with rifabutin, 0.13 with azithromycin, 0.18 with clarithromycin, and 0.23 with the azithromycin-rifabutin combination.

The annual probability of developing a new ADI was 13%.

The rate of CD4 decline was 30%.

**Measure of benefits used in the economic analysis**
The two health benefit measures used were the life expectancy and quality-adjusted life-years (QALYs). The life expectancy (in months) was derived from the Markov model. The QALYs were estimated by multiplying the quality of life associated with a specific health state by the time spent in that state. Quality values were obtained using the standard gamble approach in a sample of 69 patients with HIV disease.

**Direct costs**
A 3% discount rate was used in the base-case. The quantities and costs were not reported separately. The boundary adopted for the cost analysis was that of the health system. The charges of the hospital, physician, laboratory, home-care, and the combinations of non-protease inhibitor antiretroviral drugs, were considered. The total costs of each strategy were estimated from the Markov model. The resource use data were derived from studies published between 1991 and 1998. The price year was 1997.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were carried out on all parameters of the model. These were undertaken to investigate the uncertainty around the values derived from the literature. Specific scenarios were also examined by changing each assumption within a pre-specified range, and by changing several assumptions simultaneously.

**Estimated benefits used in the economic analysis**
In the base-case, survival was 68 months without prophylaxis, 69.4 months with rifabutin, 69.8 months with azithromycin, 69.7 months with clarithromycin, and 70 months with the azithromycin-rifabutin combination.

The number of QALYs was 44.4 without prophylaxis, 45.8 with rifabutin, 46.2 with azithromycin, 46.1 with clarithromycin, and 46.5 with the azithromycin-rifabutin combination.

**Cost results**
All prophylaxis strategies were associated with a net increase in costs when compared to no prophylaxis. In the base-case, the costs were $194,800 without prophylaxis, $199,600 with rifabutin, $201,500 with azithromycin, $206,800 with clarithromycin, and $205,200 with the azithromycin-rifabutin combination.
Synthesis of costs and benefits
The costs and benefits were combined using an incremental analysis. The results were presented with respect to QALYs. Clarithromycin was both more costly and less effective than the other strategies, and was dominated by azithromycin. In the base-case, the incremental cost per QALY was $41,500 for rifabutin compared with no prophylaxis, $54,300 for azithromycin compared with rifabutin, and $160,900 for the azithromycin-rifabutin combination compared with azithromycin alone.

The sensitivity analyses indicated that the base-case results were not affected by the discount rates (0 to 5%), quality of life values, and the efficacy of some of the drugs. However, the base-case results were sensitive to the risk of MAC and the early initiation of prophylaxis therapies. For a threshold of $75,000/QALY, the strategy of taking azithromycin remained cost-effective unless the lifetime chance of being diagnosed with MAC was less than 20%, or the rate of CD4 count decline was less than 10E6 cells/L per year.

The analyses of specific scenarios suggested that clinical factors heavily affected the incremental cost per QALY ratios. These clinical factors included the decline of CD4 count, the efficacy of protease inhibitors, the frequency and severity of resistance, and quality of life ratings. The individual cost per QALY ranged from $16,600 to $743,000.

Authors' conclusions
The analysis indicated that rifabutin and azithromycin were the most cost-effective strategies. and that the cost per QALY gained was acceptable in comparison with other medical interventions in the health care system. The incidence of Mycobacterium avium complex (MAC) was one of the most important determinants of the analysis.

CRD COMMENTARY - Selection of comparators
The authors justified the selection of the health technologies on the grounds that only those strategies established in published peer-reviewed randomised trials were selected for the analysis. You should consider whether they represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
There were insufficient details reported on the review process. In particular, no information was provided on how the studies were identified, or the criteria on which they were selected and assessed. The impact of differences between the primary studies in terms of the effectiveness estimates was not investigated. Further, although sensitivity analyses were carried out, it was unclear how the authors selected the best estimate from the range of values identified from the literature. It was also unclear how this best estimate was used in the base-case analysis.

Validity of estimate of measure of benefit
The benefit measure (QALY) used in the economic analysis was modelled using a Markov model. This model appears to have been appropriate to simulate the natural history of the disease investigated. The utility values associated with different health states were obtained from a sample of 69 patients with HIV infection. However, characteristics of this sample were not reported. In addition, the authors did not state whether these values were also valid for specific patients with advanced HIV disease.

Validity of estimate of costs
The validity of the cost analysis may have been limited by two factors. First, the estimation of costs was mainly based on charges, which do not permit a breakdown of cost per unit of resource use. Second, the authors stated that a societal perspective was adopted, but indirect costs were not included in the analysis. In addition, the authors assumed, but did not demonstrate, that non-health care expenditures were similar among the treatment strategies.

Other issues
The generalisability of the results was enhanced by conducting sensitivity analyses and assuming different scenarios.
The authors made several comparisons of their findings with those of other studies. The authors recognised that the possible side-effects of MAC-preventing therapies were not included in the model.

**Implications of the study**
The authors suggested that existing guidelines, which recommended clarithromycin as a first-line therapy, should be reconsidered. Further, as found in the USA, the incidence rates of MAC vary with geographical location. The results should, therefore, be analysed according to the place where the patients are resident.

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