Cost-effectiveness of prophylaxis against Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis undergoing immunosuppressive therapy

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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
The study examined the treatment of patients with Wegener's granulomatosis (WG), who were receiving immunosuppressive therapies with prophylactic drugs to prevent Pneumocystis carinii pneumonia (PCP). No prophylaxis was compared with combined trimethoprim (160 mg) and sulfamethoxazole (800 mg) (TMP/SMX), taken 3 times a week. No prophylaxis was also compared with a regime in which TMP/SMX was taken but, when an adverse drug reaction (ADR) occurred, the combination was replaced with aerosolised pentamidine (300 mg monthly).

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
A hypothetical cohort of patients with WG aged 35 years, just starting immunosuppressive therapy, was included in the analysis. Patients with prior allergic reactions to sulpha medications were not eligible.

Setting
The setting was not clearly stated in the model. The economic study was carried out in the USA.

Dates to which data relate
The model used data from different published articles. The articles providing effectiveness evidence were published between 1977 and 1997. The articles providing evidence on the resources were published between 1991 and 1999. The articles used to make quality of life adjustments were published between 1984 and 1996. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of the literature and the authors' assumptions.

Modelling
A Markov state-transition model was used to model the cost-effectiveness of the three different prophylaxis approaches to preventing PCP among patients with WG. The model was used to determine the clinical outcomes and the costs of the interventions. Patients were cycled through the model at one-year intervals. The health states included alive with WG, ADR, PCP, death from PCP, and death from all other causes.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the incidence of PCP without prophylaxis, with TMP/SMX prophylaxis, and with TMP/SMX followed by pentamidine;
- the incidence of ADR with TMP/SMX and with pentamidine; and
- mortality from WG, PCP and from all causes.

**Study designs and other criteria for inclusion in the review**
Not reported.

**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 stated.

**Number of primary studies included**
The effectiveness evidence was derived from nine published studies.

**Methods of combining primary studies**
A narrative method was used to combine the studies.

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

**Results of the review**
The results are presented with the ranges tested in the sensitivity analysis shown in parentheses.

The incidence of PCP was 0.85% (0.01 - 10) in WG patients receiving no drug prophylaxis against PCP, 0.09% (0.001 - 1) in patients receiving TMP/SMX, and 0.11% (0.001 - 1) in patients receiving pentamidine.

The incidence of ADR was 10% (10 - 50) in patients receiving TMP/SMX and 13% (10 - 50) in patients receiving pentamidine.

The mortality from PCP was 40.8% (10 - 90).

The mortality from WG was 5% (4.5 - 5.5) in patients aged 35 to 40 years, 2.2% (1.98 - 2.42) in patients aged 41 to 45 years, 1.8% (1.62 - 1.98) in patients aged 46 to 50 years, and 1.8% (1.62 - 1.98) in patients aged over 51 years.

The mortality from all causes was 0.19% in patients aged 35 to 45 years, 0.73% in patients aged 46 to 55 years, and 5.05% in patients aged over 56 years.

The above data were used as input parameters in the Markov model, to estimate the effectiveness of the prophylaxis strategies under investigation.
Methods used to derive estimates of effectiveness
The authors made assumptions about the quality of life adjustments used to calculate the quality-adjusted life-years (QALYs).

Estimates of effectiveness and key assumptions
The quality of life adjustment was 1 for no PCP, 0.3 (range: 0.1 - 0.9) with PCP infection, and 0.9 (range: 0.85 - 0.95) with ADR.

Measure of benefits used in the economic analysis
The measures of benefit used were the QALYs gained and the life-years gained (LYG). These were obtained from the decision model. The effect of PCP and ADR on the quality of life was calculated using authors' assumptions, following a review of the literature on the quality of life of AIDS patients. The discount rate used was 3% (0 - 5).

Direct costs
The costs were discounted at 3%. The prices were reported separately from the quantities. The costs measured were the price of a TMP/SMX (160/800 mg) tablet, the monthly cost of aerosolised pentamidine (300 mg) bronchodilators and respiratory therapy, the yearly cost of a thrice weekly regimen of TMP/SMX, the cost of a PCP episode, the cost of an ADR to TMP/SMX, and the cost of an ADR to pentamidine. The cost data were derived from actual data and published studies. The total costs of each intervention were calculated using modelling techniques. The price of the drugs was obtained from the hospital pharmacy (average wholesale price paid by the pharmacy). All the costs were expressed in 1999 US dollars, and were adjusted using the non-seasonally-adjusted medical care services of the Consumer Price Index.

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

Indirect Costs
No indirect costs were calculated.

Currency
US dollars($).

Sensitivity analysis
A one-way sensitivity analysis was carried out to investigate a number of variables. These were the cost of an ADR to TMP/SMX, the cost of an ADR to aerosolised pentamidine, the cost of PCP infection, the incidence of PCP in the three groups of patients, the quality of Life adjustment factor, the discount rate, mortality from PCP, and mortality from WG.

Estimated benefits used in the economic analysis
The discounted life expectancy (without quality adjustment) was 13.41 years with no drug prophylaxis, 13.63 years with TMP/SMX alone, and 13.73 years with TMP/SMX and pentamidine if necessary.

The QALYs were 13.36 with no drug prophylaxis, 13.54 with TMP/SMX alone, and 13.61 with TMP/SMX and pentamidine if necessary.

The side effects of treatment were not considered. The possibility that reactions to medication might change the quality
of life, but not severely enough to cease taking the medication, was not investigated.

Cost results
The total lifetime cost (discounted at 3%) was $4,538 with no drug prophylaxis, $3,304 with TMP/SMX, and $7,428 with TMP/SMX and pentamidine.

The costs of adverse effects were included.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-effectiveness analysis. In comparison with no prophylaxis, TMP/SMX was the dominant intervention, as it increased the life expectancy (0.22 years) and the QALYs (0.18 years). It was also associated with cost-savings ($1,234).

In comparison with no prophylaxis, TMP/SMX with pentamidine (when necessary) increased life expectancy. However, it was more costly, with an incremental cost per QALY of $11,560.

When TMP/SMX plus pentamidine were compared with TMP/SMX alone, the former increased the QALYs by 0.07 and cost an extra $4,124. The cost per QALY gained was $58,037.

In the sensitivity analyses, increasing the incidence of PCP in patients with WG reduced the cost of a QALY in the TMP/SMX plus pentamidine strategy. When the incidence of PCP was more than 2.25%, the TMP/SMX plus pentamidine strategy dominated the no prophylaxis strategy (cost less and increased life).

When the incidence of PCP was greater than 7.5%, the TMP/SMX plus pentamidine strategy dominated the TMP/SMX strategy, as the extra cost of pentamidine was outweighed by the increased cost of PCP.

As the number of ADRs increased, the advantage of drug prophylaxis decreased since fewer patients could benefit from reducing their risk of getting PCP. When the ADR to TMP/SMX was more than 49%, the no drug prophylaxis regime dominated the TMP/SMX alone strategy, as the QALYs were not increased. When ADRs were less than 49%, the QALYs with both drug regimes were higher than with no prophylaxis.

For all other parameters tested, the QALYs increased under the two types of drug prophylaxis considered.

The authors considered the effects of drug prophylaxis when the risk of PCP was concentrated in the first two years, and the model was run for two years. This led to an increase in the QALYs of 0.0269 for TMP/SMX and 0.0275 for TMP/SMX plus pentamidine, and a reduction in the costs of $1,606 (TMP/SMX) and $1,543 (TMP/SMX plus pentamidine), respectively. Therefore, both kinds of drug prophylaxis dominated no prophylaxis for the first two years.

Authors’ conclusions
The authors concluded that the simulation model used in their study should encourage patients with Wegener's granulomatosis (WG) to be given drug prophylaxis against Pneumocystis carinii pneumonia (PCP). As combined trimethoprim-sulfamethoxazole (TMP/SMX) was found to be dominant, there is a strong case for giving it to patients with WG who are taking immunosuppressive medication. There is an added benefit of taking TMP/SMX, in that it has been shown to reduce the rate of relapse of WG.

The authors described how TMP/SMX has improved the outlook for AIDS patients at risk of PCP. They pointed out that non-AIDS patients have a much lower rate of adverse reactions to TMP/SMX, than do AIDS patients. They also pointed out that non-AIDS patients have a higher mortality rate from PCP, and higher hospital costs associated with the diagnosis.

The advantage of taking TMP/SMX plus pentamidine depends partly on the risk of PCP. The decision as to whether or not to recommend it depends on the price that people are willing to pay for an increase in QALYs. Changing from TMP/SMX to TMP/SMX plus pentamidine makes the cost of a QALY $58,000, which is more than the standard cost-
effectiveness ratio of $50,000.

**CRD COMMENTARY - Selection of comparators**
The selection of comparator, no drug prophylaxis, was explicitly justified. It was reasonable since it represented standard practice for patients with WG receiving immunosuppressive therapy. You should assess whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The authors stated that a review of the literature had been undertaken, but did not explain how the review was conducted. In addition, they did not always explain how they selected the data from the studies that were used. In the sensitivity analyses, the authors used the variation in the estimates in the studies to test the sensitivity of their results. Due to the lack of published data, the authors also estimated some variables on the basis of their own opinion.

**Validity of estimate of measure of benefit**
The benefits were estimated by adjusting the estimates of changed life expectancy using a quality of life adjustment. This was appropriate for the patients concerned. However, the milder side effects of the medication, which were not strong enough to cause the patient to stop taking it, were not assessed.

**Validity of estimate of costs**
All the relevant direct costs were included in the analysis. The indirect costs were not included, even though the authors stated that they adopted a societal perspective in the study. However, including the indirect costs would increase the advantage of the prophylaxis treatment, as it would save the patients and their families from the time and expense that occurs when someone has PCP. The costs and quantities were reported separately for the drugs but not for the hospital costs. Information on quantities was taken from published sources and from the authors' opinions. Information on prices was taken from the hospital pharmacy and published sources. Sensitivity analyses were not conducted with respect to the unit costs. Some of the charges were used to proxy prices. The price year was reported.

**Other issues**
The authors compared their findings with those from other studies, but, according to the authors, no study has aimed to test the treatment they were studying. The issue of generalisability to other settings was not addressed. The authors presented their results fairly, focusing on most of the important variables that influenced their results. A sensitivity analysis on the price of drugs might have been interesting, especially as pentamidine is so expensive.

**Implications of the study**
The study provides strong arguments for conducting an empirical study of patients with WG, taking immunosuppressive therapy. Also, for examining the effects of prophylactic TMP/SMX, as this study on hypothetical patients found it to be a dominant strategy.

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