Practical pharmacogenetics: the cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine

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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
A screening strategy for the identification of thiopurine S-methyltransferase (TPMT), a cytosolic enzyme that catalyses the inactivation of azathioprine (AZA) in patients with rheumatologic conditions (e.g. rheumatoid arthritis and systemic lupus erythematosis), was examined. The screening strategy consisted of a validated polymerase chain reaction (PCR) test before AZA administration in order to adjust dosages in cases of reduced TPMT activity and deficiency. The dosing guidelines by TPMT genotype were as follows:

- a target dose of 2.0 to 2.5 mg/kg per day for homozygous wild type (normal TPMT activity);
- a target dose of 1.0 mg/kg per day for heterozygous (reduced TPMT activity); and
- a target dose of 0.25 mg/kg per day for homozygous mutant (deficient of TPMT activity).

The reduced dosage avoided the development of haematological cytopenia, the most serious toxicity of AZA.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with rheumatoid arthritis or systemic lupus erythematosis who were receiving AZA.

Setting
The setting was secondary care. The economic study was conducted in Canada.

Dates to which data relate
The effectiveness data were estimated from studies published between 1997 and 2001. No dates for the resource use data were reported. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.
Modelling
A decision tree model was constructed to assess the costs and outcomes associated with and without testing in patients receiving AZA therapy for rheumatologic conditions. Two main branches were considered, normal dosing and genotype dosing. The probability of developing haematological cytopenia was considered only in the normal dosing arm. The time horizon of the model was 6 months.

Outcomes assessed in the review
The outcomes assessed were the rate of haematological cytopenia, and the sensitivity and specificity of the PCR genotype test.

Study designs and other criteria for inclusion in the review
One of the primary studies was a systematic review of three clinical trials, but the designs of the remaining studies were not reported. Information (sample size and dosages) on other studies was also provided, although their estimates were not explicitly used in the decision model.

Sources searched to identify primary studies
MEDLINE, EMBASE, Pre-MEDLINE and the Cochrane Database of Systematic Reviews were searched from 1966 to September 2000 for relevant English language literature. The keywords used were "AZA", "TPMT", "polymorphisms", "rheumatoid arthritis", "rheumatology", "systemic lupus erythematosus", "leukopenia" and "pancytopenia". The references from retrieved articles were also searched manually.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Three primary studies were included in the review.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The rate of haematological cytopenia was 0.09 (range: 0.03 - 0.15).

The sensitivity of the PCR genotype test was 95.2% (range: 76.2 - 99.9) and the specificity was 100% (range: 83.9 - 100).

Measure of benefits used in the economic analysis
The summary benefit measure used was the number-needed-to-treat (NNT) to avoid one adverse event over 6 months. This was used to reflect the clinical end point of avoidance of haematological cytopenia. It was derived from the
decision model.

Direct costs
Discounting was not relevant since the costs were incurred during a timeframe of 6 months. The unit costs were not presented separately from the quantities of resources used for all items. The health services included in the economic evaluation were inpatient and outpatient care, PCR testing, management of treatment failure, and AZA therapy. A pharmacist dispensing fee per episode was also included. The cost/resource boundary of the third-party payer was adopted. The costs were estimated from published studies, average wholesale prices, and Canadian databases of provincial costs. The cost of the PCR genotyping test was unavailable and, therefore, was based on the costs of other PCR tests available in other settings. The resource use data were based on experts’ assumptions. The price year was 1999.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
Canadian dollars (Can$). The conversion rate from Canadian dollars into US dollars ($) was Can$1 = $0.67.

Sensitivity analysis
Univariate and threshold sensitivity analyses were conducted to assess the robustness of the results of the analysis to variations in several model inputs. The model inputs investigated were the probability of avoidable cytopenia, the cost of PCR, the probability of inpatient care, and the sensitivity and specificity of the PCR test.

Estimated benefits used in the economic analysis
The NNT to avoid one adverse event over 6 months was 20.

Cost results
The estimated costs per patient were Can$677 with the normal dosing strategy and Can$663 with the genotype-directed dosing strategy.

Synthesis of costs and benefits
The costs and benefits were combined by calculating an incremental cost-effectiveness ratio. However, the incremental cost-effectiveness ratio was not actually estimated because the genotype-directed dosing strategy dominated the normal dosing strategy, which was both less effective and more costly.

The sensitivity analysis showed that the results were sensitive to the cost of PCR. At a value of Can$114, the two strategies had equal costs. The genotype-directed dosing strategy was cheaper than the normal dosing strategy when the probability of preventable cytopenia was above 4.4%, and when the probability of receiving inpatient care was above 44%.

Authors’ conclusions
The determination of thiopurine S-methyltransferase (TPMT) activity through genotyping, and the subsequent azathioprine (AZA) dose reduction in susceptible individuals, was cost-effective (and also cost-saving under some
conditions) from the perspective of the Canadian third-party payer. Drug-related toxicity was reduced at a modest extra cost in comparison with standard AZA dosing without testing.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear, as no PCR-based screening represented the current strategy for patients receiving AZA therapy for rheumatologic conditions. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a well-conducted review of the literature. The sources searched and the approach used were reported. However, only the design of one of the primary studies was reported. Details of samples and dosages were provided for other studies, which were not directly used in the model. It was not stated whether the primary studies were comparable, and the methods used to extract and combine the estimates were not described. This introduced some uncertainty into the estimates used in the model. Some of these estimates were then varied in the sensitivity analysis.

**Validity of estimate of measure of benefit**
The summary benefit measure was selected to reflect the impact of the intervention on the patients' health through avoidance of the most severe adverse reaction. The use of NNT is not often used in the literature. Hence, it may be difficult to compare with the benefits of other health care interventions. The time horizon of the model (i.e. 6 months) appears to have been appropriate for establishing the effectiveness of screening.

**Validity of estimate of costs**
The perspective adopted in the study was explicitly stated. It appears that all the categories of costs relevant to this perspective have been included in the analysis. A breakdown of the costs was provided. The unit costs and the quantities of resources used were not presented separately for all items. Ranges of values were provided but no statistical tests on the costs were conducted. The price year was reported, which facilitates reflation exercises in other settings. Information on resource use was mainly based on experts' opinions, which were not tested in the sensitivity analysis. The cost estimates were specific to the study setting.

**Other issues**
The authors stated that their study was the first to assess the cost-effectiveness of TPMT screening before AZA therapy, although economic evaluations of genomic testing before drug therapies had been published and, in general, had supported the cost-effectiveness of pre-treatment screening. Clearly, in a scenario in which TPMT screening was used as a confirmatory mechanism once toxicity had developed, the cost-effectiveness of PCR testing would be completely different. The issue of the generalisability of the study results to other settings was not explicitly addressed and few sensitivity analyses were conducted. This affected the external validity of the analysis. The study involved patients with rheumatologic conditions and this was reflected in the authors' conclusions.

**Implications of the study**
The study results should support decision-makers in adopting a screening strategy to identify TPMT polymorphisms prior to AZA treatment. The authors suggested that future studies should assess health-related quality of life and should include indirect costs, which would further enhance the cost-effectiveness of TPMT genotype testing before AZA therapy.

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Other publications of related interest


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