Pharmacoeconomic analysis of thiopurine methyltransferase polymorphism screening by polymerase chain reaction for treatment with azathioprine in Korea

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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 genotype-based dosing by polymerase chain reaction (PCR) screening for thiopurine methyltransferase (TMPT) polymorphism and treatment with azathioprine. The health technology falls under the umbrella of pharmacogenetics, which involves the study of pharmacological response and its modification by hereditary influence. Full details of azathioprine dosage used the intervention (based on the Physician's Desk Reference guidelines and other reports), and the comparator technology, were provided in the paper.

Type of intervention
Screening and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of adult patients (50 kg body weight) with moderate to severe RA or SLE, who required azathioprine treatment because of the unsuitability of methotrexate or cyclophosphamide.

Setting
The setting was not stated. The economic study was conducted in Korea.

Dates to which data relate
The effectiveness data related to studies published between 1980 and 1997. The resource use data on drugs and laboratory fees were for 2002, whilst the dates for other resources (hospitalisation) were not provided. A unitary price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of studies.

Modelling
A decision analytical model was used. Although the software used was not stated, a graphical representation was provided with clearly marked parameters and their values. The outcomes, in terms of costs and effectiveness, were provided for each terminal node and the tree as a whole. The time horizon of the model was one year. The authors made a number of structural assumptions about the "basic scenario" considered, and these were clearly and fully reported in the paper.
Outcomes assessed in the review
The input parameters for the model, which were derived from the literature, were:

the prevalence of TPMT activities;

the sensitivity and specificity of PCR genotyping; and

the incidence rate of severe adverse reactions from intermediate activity.

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

Sources searched to identify primary studies
Not stated.

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
Four studies and an unspecified number of reports were used.

Methods of combining primary studies
For the base-case analysis, the authors selected the most frequently cited and feasible values found in the literature. The discarded values were used to inform the sensitivity analysis.

Investigation of differences between primary studies
Not stated.

Results of the review
In the base-case, the prevalence of decreased TPMT activity was 11.3%.

The severe adverse event rate was 2.94% for conventional weight-based dosing and 0.1% for genotype-based dosing.

The sensitivity of PCR was 96.3% and the specificity was 100%.

Measure of benefits used in the economic analysis
The measure of benefit was the probability of not dropping out of treatment because of serious adverse events. This was derived from the model, based on the effectiveness results reported (above).

Direct costs
The costs and the quantities were not reported separately. Only direct costs were used, which included costs to the patient and the health care system. More specifically, drug costs, laboratory tests, PCR costs, hospitalisation costs (for
severe bone marrow toxicity as a result of azathioprine treatment), blood and platelet transfusions, use of granulocyte colony-stimulation factor, antibiotics and isolation room fees during the hospital stay. Discounting was not applied, but this was appropriate as the time horizon for the analysis was one year. The direct costs for PCR and hospital admissions were obtained from actual data. Other cost data were obtained from prior reports. The drug costs and laboratory test fees were based on the 2002 Korean insurance system. A single price year was not reported.

**Statistical analysis of costs**
No statistical analysis of the costs was conducted.

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

**Currency**
Korean won and US dollars ($). The exchange rate was $1.00 = 1,193 Korean won.

**Sensitivity analysis**
One-way sensitivity analyses were conducted to assess the variability and uncertainty in the parameters used in the modelling. The parameters varied were the prevalence rates of TPMT activities, admission costs, PCR cost and the incidence rates of severe adverse reactions resulting from intermediate activities. The ranges were derived from the literature or, in cases where data were not available, wide ranges were utilised (e.g. on the cost of PCR).

**Estimated benefits used in the economic analysis**
The probability of not dropping out of treatment because of serious adverse events was 97.06% for conventional weight-based dosing and 99.9% for the genotype-based dosing.

**Cost results**
In the base-case solution the total expected cost was 1,339 x10^3 Korean won ($1,117) for conventional weight-based dosing and 1,109 x10^3 Korean won ($926) for the genotype-based dosing.

**Synthesis of costs and benefits**
The authors intended to calculate an incremental cost-effectiveness ratio. However, the base-case solution indicated that the genotype-based dosing strategy dominated conventional weight-based dosing (i.e. it was more effective and less costly). The findings of the sensitivity analyses, for all variations in model parameters examined, showed that genotype-based dosing always dominated the comparator.

**Authors’ conclusions**
The genotype-based dosing strategy through thiopurine methyltransferase (TPMT) was less costly and more effective, in terms of a reduction in the number of serious adverse events, than the conventional weight-based dosing strategy in Korea.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clearly presented. Conventional weight-based dosing was stated to be the conventional approach. Other potential comparator technologies (particularly biochemical assay) were also discussed and reasons for their non-inclusion were given. You should determine if the intervention and the chosen comparator are relevant to your own setting.
Validity of estimate of measure of effectiveness
The effectiveness data used in the construction of the model appear to have been valid, although there was no evidence that a systematic review of the literature was undertaken to derive the estimates. However, the authors did provide a critique of other available literature and gave some indication as to why particular studies were selected (e.g. prevalence data are race-dependent, therefore data appropriate for the Korean population were chosen). To address the uncertainty in the estimates used in the modelling, appropriate sensitivity analyses were undertaken and these enhance the validity of the findings.

Validity of estimate of measure of benefit
The benefit measure chosen was appropriate for the study population. However, being condition-specific, it has limitations in terms of facilitating comparisons with other health care programmes, as would have been the case if quality-adjusted life-years or other utility-based health outcomes had been used.

Validity of estimate of costs
The authors stated that a societal perspective was used in the cost analysis. However, it would appear that only the direct costs to the health care system and patient were included. In order for it to represent a true societal perspective, the costing would have needed to include productivity losses. The costing was clearly presented and all the resources satisfactorily itemised, along with their sources. Although a price year was given for some cost data, the year(s) to which other data referred was not clear. Whilst these limitations in the cost data clearly exist, sensitivity analyses were appropriately conducted, thus increasing the generalisability of the results.

Other issues
The authors made appropriate comparisons with other studies, citing only one other study on the cost-effectiveness of the intervention from a Canadian context, and another cost study that had limitations as it assumed perfect sensitivity and specificity for PCR. The authors stated that this was the first study of its type for a Korean population. The authors addressed the issue of generalisability in discussions about factors that would influence the generalisability of results determined in other countries with different epidemiological profiles (e.g. prevalence data). The authors summarised the limitations of their study. First, only direct medical costs were calculated (although the inclusion of indirect costs would have strengthened the validity of the cost results). Second, sensitivity analyses were not undertaken on the sensitivity and specificity of PCR (stable laboratory conditions were assumed). Finally, the chosen scenario and assumptions of the model may not reflect actual clinical practice.

Implications of the study
In terms of clinical practice, the findings of the study suggested that genotype-based dosing through TPMT is highly cost-effective in comparison with weight-based dosing. The authors indicated that their model could be used to evaluate the cost-effectiveness of the intervention or comparator in other ethnic and racial groups (with different epidemiological profiles).

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