A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine

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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 compared four management strategies addressed at patients with Crohn's disease (CD). The strategies compared were community care (CC), thiopurine methyltransferase (TMPT) screening, metabolite monitoring (MM), and TMPT screening plus MM (TMPT+MM).

CC: patients were administered the lowest dose of azathioprine (AZA) (i.e. 50 mg), with the dose increased to 100 mg if a patient had no clinical response within 3 months.

TPMT screening: all patients had TPMT screening and their initial dosing was subsequently based on their TPMT genotype. Patients with TPMT wild-type genotype received 100 mg AZA, TPMT intermediate genotype patients received 50 mg AZA, while TPMT deficient genotype patients did not receive AZA and were administered methotrexate (MTX, 25 mg).

MM: patients were initially administered an AZA dose of 50 mg. At 4 weeks, patients with normal white blood count (WBC) had their metabolite levels checked. Subsequently, metabolite levels were checked in patients with WBC >4,000 every 8 weeks until week 52 if they did not respond to treatment, and the AZA dose was adjusted accordingly.

TPMT+MM: as in the TPMT screening alone strategy, the patients' initial AZA dose was dependent on their TPMT genotype. MM was carried out at 4 weeks of treatment in order to determine whether patients would undergo an AZA dose adjustment (decrease or increase).

All patients received steroid therapy at a dose of 20 mg/day until a Crohn's Disease Activity Index (CDAI) of less than 150 was reached. After documentation of clinical response to AZA or MTX treatment, steroid use was gradually diminished at a rate of 2.5 mg per dose per week within the next 8 weeks. Patients on infliximab did not have their steroid dose decreased.

Type of intervention
Screening and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The target population comprised adult patients (age 18 years and older) who suffered from moderate to severely chronically active steroid-treated CD and had a CDAI between 150 and 450.

Setting
The setting was a clinical practice setting (secondary care). The economic analysis was carried out in the USA.
Dates to which data relate
The effectiveness results were derived from studies published between 1980 and 2002. The cost data were derived from official sources published between 2000 and 2004. All costs were reported for the price year 2004.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies. In cases where data could not be obtained from the literature, effectiveness data were based on expert opinion and authors’ assumptions.

Modelling
The authors constructed a decision analytic model using DATA 4.0 for Healthcare (TreeAge Software Inc., Williamstown) to evaluate the cost-effectiveness of the four strategies. The time horizon of the model was 1 year. The model was based on various assumptions about efficacy, safety, drug dosing and costs, which were all reported in the current study. However, they were too numerous to be reported here.

Outcomes assessed in the review
The authors reported that a systematic review of the literature was undertaken.

For the CC strategy, the TPMT screening strategy with patients with normal genotype and the MM strategy, the input parameters used in the model were:

- the probability of WBC 3,000 - 4,000 at week 2, and the probability of WBC 3,000 - 4,000 at week 2 and WBC <4,000 at week 4;
- the probability of WBC 3,000 - 4,000 at weeks 4, 8 and 12;
- the probability of WBC <3,000 at weeks 2, 4, 8 and 12; and
- the probability of WBC <4,000 at weeks 8, 12, 16, 24, 32, 40 and 48, and after dose increase due to nonresponse.

Within the TPMT intermediate genotype strategy, the probabilities used were:

- the probability of WBC 3,000 - 4,000 at week 2;
- the probability of WBC 3,000 - 4,000 at week 2 and WBC <4,000 at week 4;
- the probability of WBC 3,000 - 4,000 at weeks 4, 8 and 12; and
- the probability of WBC <3,000 at weeks 2, 4, 8 and 12.

WBC probability-values equaled the probability of being on a specific AZA dose amount at the identified time period multiplied by the risk of leucopenia at WBC <3,000 or <4,000.

The following response rate probabilities were included:

- response rate with a dose decrease and a dose increase of 50 mg AZA;
- response rate to initial dose of AZA;
- response rate to initial sub-optimal dose of AZA;
- sustained response rate 8 weeks after initial response (CDAI <150 and off steroids);
- sustained response rate 16 weeks after initial response (CDAI <150 and off steroids);
response rate to remicade;

response rate for initial nonresponders to remicade becoming responders 4 weeks after; and

nonresponders with a metabolite level lower than 235 pmol/8 x10^8.

The probabilities included for sepsis were diagnosis of sepsis with WBC <3,000 and discontinuation of AZA, and dying from sepsis. Additional probabilities for alternative strategies were the probability of being TPMT genotype deficient, TPMT genotype intermediate and TPMT genotype wild-type, and the probability of a metabolite level lower than 235 pmol/8 x10^8.

Study designs and other criteria for inclusion in the review
The study designs included in the review were not reported. The authors reported that English-language articles published from the mid 1960s to June 2002 were identified. The Medical Subject Heading terms used in the search were "Crohn's Disease", "azathioprine", "6-mercaptopurine", "metabolite monitoring", "thiopurine methyltransferase", "serodiagnostic testing", "leukopenia", "hepatotoxicity", "quality adjusted life years", "QALYs", "utility measurement", "standard gamble", "time trade-off", "preference" and "economics".

Sources searched to identify primary studies
The authors searched the PubMed and HealthSTAR databases. In addition, the bibliographies of key articles were checked for additional (secondary) references.

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 authors used 13 studies as sources of effectiveness evidence.

Methods of combining primary studies
Due to the limited number of studies with available data for each model probability, the authors did not use a method to combine the results of the individual primary studies.

Investigation of differences between primary studies
It would appear that differences between the primary studies were not investigated.

Results of the review
The probability values for WBC for all strategies were too numerous to report here.

It was reported that the WBC values for the TPMT intermediate genotype strategy were assumed to be 50% lower than the WBC probability values for the CC, TPMT normal/high genotype and MM strategies.

The response rate to the initial dose of AZA was 0.54.

The response rate to the initial sub-optimal dose of AZA was 0.32.
The sustained response rate 8 weeks after initial response (CDAI <150 and off steroids) was 0.65.
The sustained response rate 16 weeks after initial response (CDAI <150 and off steroids) was 0.73.
The response rates to remicade and nonresponders with a metabolite level lower than 235 pmol/8 x10^8 were 0.60.
Diagnosis of sepsis with WBC <3,000 and discontinuation of AZA was 0.18.
The probability of dying from sepsis was 0.40.
The probability of a TPMT deficient genotype was 0.003, of a TPMT intermediate genotype 0.107, and of a TPMT wild genotype 0.890.
The probability of a metabolite level lower than 235 pmol/8 x10^8 was 0.40.

Methods used to derive estimates of effectiveness
Some effectiveness estimates were based on expert opinion. In addition, the authors made several modelling assumptions about efficacy, safety, and drug dosing.

Estimates of effectiveness and key assumptions
The following estimates of effectiveness were based on expert opinion:

- the response rate with a dose decrease and a dose increase of 50 mg AZA was 0.50; and
- the response rate for initial nonresponders to remicade becoming responders 4 weeks after was 0.20.

Model assumptions are too numerous to be reported here. They were all well reported in the current study.

Measure of benefits used in the economic analysis
The authors used time to response and time to sustained response as the measures of benefits. Time to response corresponded to the elapsed time (in weeks) from initiation of AZA until a patient first responds to treatment (achieves CDAI <150 with or without steroids). Time to sustained response corresponded to the elapsed time (in weeks) from the start of AZA until the patient was able to stay in response (CDAI <150) and remain off steroids 16 weeks after initial response.

Direct costs
The health service costs included in the analysis were the annual drug costs of azathioprine (25 and 50 mg/day doses), methotrexate (25 mg/week, including costs of syringe and needle), prednisone (20 mg/day), prednisone (8-week weaning, assuming 20 mg/day during week 1 until 2.5 mg/day at week 8) and infliximab (assuming a 70-kg person and a dose of 5 mg/kg). The costs of the initial office visit (high complexity/consult), follow-up office visit, office visit, CBC manual test costs, MM, TPMT screening, initial hour of intravenous infusions, 2 additional hours of infusion, sepsis and surgery were also assessed.

The costs and the quantities were reported separately. The cost estimates were derived from official published sources, while the quantities of resources used were derived from the model. Discounting was not relevant as the time horizon of the model was 1 year. All costs were appropriately adjusted and reported for the price year 2004.

Statistical analysis of costs
The costs were treated deterministically.
Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The authors conducted various one- and two-way sensitivity analyses to investigate the robustness of the results to variability in the data. The parameters investigated in the one-way sensitivity analysis were drug costs (e.g. AZA, MTX, infliximab), procedural costs (TPMT screening, MM and surgery), and probabilities of sepsis (diagnosis of sepsis with WBC <3,000 and discontinuing AZA and death due to sepsis), metabolite level and dose response. Two-way sensitivity analyses were conducted on costs (i.e. drug costs) and probabilities of sepsis, metabolite level and dose response. All probabilities and costs were varied +/- 50% from base-case values while 3-fold AZA drug costs were used.

Estimated benefits used in the economic analysis
The CC strategy achieved response (sustained response) in 22.41 (45.36) weeks, the TPMT alone strategy in 19.10 (42.91) weeks, the TPMT+MM strategy in 18.96 (39.80) weeks, and the MM strategy alone in 18.66 (39.83) weeks. An incremental effectiveness analysis was performed. Compared with CC, TPMT alone resulted in a 3.31-week reduction in time to response, TPMT+MM resulted in a 3.45-week reduction, and MM alone resulted in a 3.75-week reduction. Again, compared with CC, TPMT alone resulted in a reduction of in time to sustained response of 2.45 weeks, TPMT+MM in a 5.56-week reduction, and MM alone in a 5.53-week reduction.

Cost results
The total costs were reported per patient. The CC strategy had a total cost of $7,142, the TPMT alone strategy $3,861, the TPMT+MM strategy $5,877, and the MM strategy alone $6,441. An incremental analysis of the costs demonstrated that, compared with CC, TPMT alone resulted in cost-savings of $3,281, TPMT+MM in cost-savings of $1,264, and MM alone in cost-savings of $700.

Synthesis of costs and benefits
A cost-effectiveness ratio was not calculated since all three strategies proved to be less costly and more effective (in terms of time to response and time to sustained response) in comparison with the CC strategy. Sensitivity analyses demonstrated that the results were robust to variability in the data.

Authors' conclusions
"The addition of alternative strategies to CC (community care) may improve AZA (azathioprine) outcomes and reduce the total cost of care for steroid treated chronically active CD (Crohn's disease) patients, with TPMT (thiopurine methyltransferase) being more beneficial for initial response to treatment and MM (metabolite monitoring) being more beneficial for sustained response to treatment."

CRD COMMENTARY - Selection of comparators
The selection of the comparators was explicitly justified. You should decide if this represents a valid health technology in your own setting.
Validity of estimate of measure of effectiveness
The authors reported that a systematic review was undertaken to identify health and economic outcomes. However, it was unclear if the review was conducted in a satisfactory way to identify relevant research and minimise biases. For example, estimates of effectiveness from the available studies were not combined and the data used selectively, while differences between the primary studies were not investigated. Although some effectiveness estimates were based on expert opinion and authors’ assumptions, the methods used to derive these estimates of effectiveness were not reported. However, extensive sensitivity analyses were conducted, which improves both the internal validity of the study and the generalisability of the results.

Validity of estimate of measure of benefit
The authors used time to response and time to sustained response as measures of benefits in the economic analysis. These were derived from the model.

Validity of estimate of costs
The perspective of a third-party payer was adopted in the economic analysis. It appears that all the relevant categories of costs were included in the analysis. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. All costs were derived from official published sources. The costs were treated deterministically, but sensitivity analyses were conducted to assess the robustness of the estimates used. Appropriate adjustments were carried out and the price year was reported. Discounting was not carried out, which was appropriate given the short time horizon (less than 2 years).

Other issues
The authors compared their findings with a published study and generally found them to be in agreement. The issue of generalisability of the results was not explicitly addressed. The study enrolled patients with steroid treated chronically active CD and this was reflected in the authors’ conclusions. The authors do not appear to have presented their results selectively.

The authors reported several limitations to their study. For instance, they reported that the impact of TPMT screening was restricted by the fact that the difference in the state of leucopenia events compared with the CC strategy was small. The authors felt that if cost and utility of sepsis and death had been included as measures of safety, the TPMT strategy would have resulted in increased safety. Given the lack of published data, various effectiveness probabilities were based on expert opinion, which may be of limited value. It was not possible to conduct a cost-utility analysis or evaluate the impact on quality of life, owing to the lack of health utility data available in the literature. The authors adopted a conservative approach, thus the option of "evidence based dosing" documented in the literature was not accounted for in the model.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice, or the need for future research. However, the discussion indicated areas where more research-based information is needed.

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None stated.

Bibliographic details

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