Thiopurine S-methyltransferase testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis

Hagaman JT, Kinder BW, Eckman MH

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.

CRD summary
This study assessed the cost-effectiveness of testing the level of the enzyme thiopurine S-methyltransferase (TPMT) in the blood, before treatment with azathioprine, for patients with idiopathic pulmonary fibrosis. The authors concluded that TPMT testing before treatment was cost-effective. The methods and the reporting of the results were satisfactory. Some limitations were reported and should be considered, but the conclusions reached by the authors appear to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to assess the costs and effects of testing for the amount of the enzyme thiopurine S-methyltransferase (TPMT) in the blood, prior to treatment with azathioprine, to limit bone-marrow toxicity, for patients with idiopathic pulmonary fibrosis (IPF), a common form of idiopathic interstitial pneumonia. The hypothetical cohort of patients was based on those in a study of 14,545 Spanish patients with diseases treatable by azathioprine and with varying levels of TPMT activity (Gisbert, et al. 2007, see ‘Other Publications of Related Interest’ below for bibliographic details).

Interventions
TPMT testing was compared against no testing, which was followed by treatment with azathioprine, acetylcysteine, and prednisone; and against no drug treatment, which was conservative management with supportive measures only. The TPMT test defined patients as having low, moderate, or high activity. Those with low activity received no drug treatment, moderate activity received a reduced dose of azathioprine, and normal activity received the normal azathioprine combination treatment.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A decision-analytic model synthesised the data from relevant, available published studies, using some assumptions. The outcomes were assessed over one year and the authors did not report the study perspective.

Effectiveness data:
The clinical effectiveness outcomes were IPF disease progression, defined as a reduction in the forced vital capacity by at least 10%; and the presence of leucopenia, a side-effect of azathioprine. The results of the test for TPMT activity were from the large Spanish study that defined the cohort (Gisbert, et al. 2007). The efficacy data for azathioprine were from this and other studies, including one randomised controlled trial. The leucopenia estimates were from relevant published studies. An expert panel of pulmonologists, specialising in the treatment of interstitial lung disease, provided the estimates for associated therapies and complications.

Monetary benefit and utility valuations:
The utility values for IPF progression, leucopenia, and complicated leucopenia were from four published studies.
Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs).

Cost data:
The direct medical costs were included for the TPMT assay, medications, and adverse events, including hospitalisations, procedures, and physician visits. The unit costs were from national schedules and the medications were valued at retail prices. All costs were reported in US dollars ($) at 2007 values.

Analysis of uncertainty:
The model parameters were examined in one-way and two-way sensitivity analyses, using a range of values set by the authors, and the results were illustrated in line graphs.

Results
Over one year, the total costs were $9,691 for no treatment, $15,802 for normal treatment, and $15,818 for TPMT testing. The QALYs were 2.50 for no treatment, 2.61 for normal treatment, and 2.62 for TPMT testing.

Compared with no treatment, normal treatment was excluded due to extended dominance as it was less cost-effective than a more effective strategy. TPMT testing had an incremental cost-utility ratio of $49,156. Compared with normal treatment, the ratio for TPMT testing was $29,663.

These results were sensitive to the frequency of TPMT alleles and disease progression. The abnormal TPMT activity had to be over 13.5% for TPMT testing to produce more QALYs and lower costs than normal treatment. When the probability of leucopenia was over the base case value of 10%, TPMT testing was more expensive, compared with normal treatment and when over 12%, TPMT testing was no longer cost-effective at a $50,000 per QALY willingness-to-pay threshold.

Authors’ conclusions
The authors concluded that TPMT testing before starting treatment with azathioprine, acetylcysteine, and steroids was cost-effective for patients with IPF.

CRD commentary
Interventions:
The three strategies were briefly described; the normal and reduced doses for azathioprine were not stated. The strategies appear to have been appropriate comparators and the usual care (treatment without testing) was included.

Effectiveness/benefits:
The effectiveness data appear to have been from reasonable-quality published studies, but the publications should be consulted to assess the internal validity of the data. There was no report that a systematic review was undertaken, which means that all the best available evidence might not have been included. The performance or accuracy of the TPMT test was not discussed and this could have affected the results or been varied in the sensitivity analyses. The valuation methods for the utilities were not reported and their quality is uncertain.

Costs:
The perspective was not stated and it was unclear whether the health provider or the patient would pay for the genetic test. The resource costs were from publicly available sources. Discounting was appropriately not performed, as the time horizon was only one year. The costs seem to have been appropriately adjusted for inflation.

Analysis and results:
The analytic approach was satisfactorily reported and the results were combined in a full incremental analysis. The results of the one-way sensitivity analyses were not fully reported. A comprehensive probabilistic sensitivity analyses could have fully assessed the uncertainty in the findings. The authors reported a number of limitations to their study including their reliance on non-randomised studies and the assumptions made, such as assuming the same efficacy for normal- and reduced-dose azathioprine.
Concluding remarks:
The methods and the reporting of the results were satisfactory. The limitations of the study should be considered, but the conclusions reached by the authors appear to be appropriate.

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