Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease


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
The study assessed the cost-effectiveness of two anti-TNF-alpha agents (infliximab and adalimumab) for treatment of refractory Crohn's disease. The authors concluded that neither anti-TNF-alpha was cost-effective from the perspective of the public payer for management of refractory Crohn's disease because of the high cost of treatment compared to usual care. The analysis was transparent and based on robust cost-effectiveness methodology. The authors’ conclusions appear valid.

Type of economic evaluation
Cost-utility analysis

Study objective
The study assessed the cost-effectiveness of two anti-TNF-alpha agents (infliximab and adalimumab) for treatment of refractory Crohn's disease in adult patients with a Crohn's Disease Activity Index (CDAI) of 200 or more.

Interventions
The treatments under examination were infliximab and adalimumab. The background comparator was usual care, which referred to various conventional non anti-TNF-alpha treatments that included corticosteroids and other immunosuppressants. Infliximab induction therapy comprised infusions of 5mg/kg at weeks zero, two and six. Infliximab maintenance therapy comprised infusions of 5mg/kg every eight weeks. Adalimumab induction therapy comprised a 160mg subcutaneous injection at week zero and an 80mg subcutaneous injection at week two. Adalimumab maintenance therapy comprised 40mg subcutaneous injections every two weeks.

Location/setting
Canada/secondary care.

Methods
Analytical approach:
The analysis was based on a Markov model with a time horizon of five years. The perspective was that of a publicly funded health care system.

Effectiveness data:
Clinical sources of inputs were derived from a systematic review of the literature, the methods and results of which had been presented extensively in a published health technology assessment. Efficacy (remission and response rates) of the two biologic treatments was a key input of the model taken from published clinical trials (none were head-to-head). Each trial provided a specific model input. Placebo arms of the trials were used to estimate the efficacy of usual care arms. Some adjustments were required to pool evidence for the usual care strategy because of differences in the placebo arms of the trials. Other inputs were taken from additional clinical trials and review studies.

Monetary benefit and utility valuations:
Utility valuations were taken from a previous study that used the standard gamble methodology in a sample of Crohn’s disease patients.

Measure of benefit:
Quality-adjusted life-years (QALYs) were used as the summary benefit measure and were discounted at an annual rate of 5%.

Cost data:
The economic analysis included the costs of initial anti-TFN-alpha treatment, maintenance anti-TFN-alpha treatment, non anti-TFN-alpha outpatient medications and surgery. Drug costs were derived from the manufacturer (infliximab) or official reimbursement rates in three Canadian provinces (adalimumab). A pharmacy mark-up was applied. Costs of chest X-ray, tuberculosis skin test and hepatitis B blood test (performed before the first anti-TFN-alpha treatment) were derived from a hospital participating in the Ontario Case Costing Initiative (OCCI). Quantities of other drugs used in Crohn’s disease patients were based on expert opinion and valued using the Ontario Drug Benefit Formulary. The OCCI database was used to estimate in-patient costs. Surgical costs were estimated using official reimbursement rates. A 5% annual discount rate was applied. Costs were reported in Canadian dollars ($). The price year was not reported explicitly.

Analysis of uncertainty:
One-way sensitivity analyses were carried out to investigate the impact of model assumptions, especially those related to patient weight. Alternative sources were used for some inputs. The overall issue of uncertainty was assessed using a probabilistic sensitivity analysis based on 1,000 Monte Carlo simulations and conventional distributions for model inputs. Cost-effectiveness acceptability curves were generated.

Results
Projected costs and QALYs were $17,107 and 2.555 with usual care, $45,480 and 2.701 with adalimumab and $54,084 and 2.721 with infliximab. Compared with usual care, the incremental cost per QALY was $193,305 with adalimumab and $222,955 with infliximab. The incremental cost per QALY gained with infliximab over adalimumab was $451,165.

The sensitivity analysis showed that both adalimumab and infliximab cost-effectiveness ratios remained higher than $100,000 in all circumstances expect for a reduction of 50% in adalimumab drug cost. The probabilistic sensitivity analysis showed that adalimumab had the greatest probability of being cost-effective at a willingness to pay of $208,000 or more.

Authors' conclusions
The authors concluded that neither anti-TFN-alpha agent was cost-effective from the perspective of the public payer for the management of refractory Crohn’s disease given the high cost of treatment compared with usual care.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear as infliximab and adalimumab were the two licensed anti-TFN-alpha agents for the management of refractory Crohn’s disease in Canada. Both were appropriately compared against usual care, which included several possible treatments often grouped in a single class in most studies. These treatments are generalisable to other health care settings.

Effectiveness/benefits:
Clinical inputs were selected on the basis of a systematic review of the literature that should have ensured the inclusion of the most relevant studies. Treatment effect was taken from valid sources that were mostly clinical trials (generally considered the highest level of data quality for internal validity). No head-to-head trials between the two anti-TNF-alpha options were available and the results of the comparison between adalimumab and infliximab should be treated with caution given differences among studies in the indirect comparison. Adjustments were made to partially deal with this issue. Also, extensive sensitivity analysis was conducted on model parameters that showed the robustness of the base case findings. QALYs were an appropriate benefit measure for this study population. No differences in mortality were considered. Utility weights were taken from a published study that had used a valid instrument to elicit preferences.

Costs:
The economic analysis was carried out satisfactorily. Extensive details of unit costs and resource quantities were
presented, especially for anti-TNF-alpha drugs. Data sources were clearly reported for all items and most estimates appeared to have been based on official rates in the Canadian setting. Variations in economic inputs were considered in the sensitivity analyses. The included cost categories reflected the perspective of the public payer. The authors acknowledged that a societal perspective would have improved the cost-effectiveness of the anti-TNF-alpha options. Reflation exercises in other time periods were not feasible as the price year was not reported.

Analysis and results:
The expected costs and benefits were presented clearly. They were synthesised using an incremental analysis and the efficiency frontier. The structure, pathways and assumptions of the decision model were described clearly. Specifically, the authors justified exclusion of adverse events related to injections (because of their small impact on the health and economic outcomes) and mortality (not the main outcome in clinical studies of Crohn’s disease and not relevant given the relatively short time horizon of the model). Appropriate sensitivity analyses were carried out to identify drivers of the model and to examine the robustness of health and economic outcomes. Study results were likely to be relevant in other settings with similar relative drug prices.

The authors compared their results with those of other published studies and found similar results except for a study conducted in the UK that found use of anti-TNF-alpha agents cost-effective with a lifetime horizon and different assumptions.

Concluding remarks:
The analysis was transparent and based on robust cost-effectiveness methodology. The authors’ conclusions appear valid.

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