Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis

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
Etanercept (25 mg twice weekly) and infliximab (5 mg/kg every 6 weeks after the usual loading dose at weeks 0, 2, and 6), two tumour necrosis factor alpha (TNF-alpha) inhibitors used for the treatment of active ankylosing spondylitis (AS), were studied.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with AS, defined as a Bath ankylosing spondylitis disease activity index (BASDAI) score of 4 or more.

Setting
The setting was secondary care and a hospital. The economic study was carried out in the Netherlands.

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2003. Some resource use and costs were estimated from a longitudinal study published between 2001 and 2003. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model with 3-month cycles and a 5-year time horizon was used to assess the clinical and economic outcomes associated with each of the two TNF-alpha inhibitors in comparison with usual care as treatment options for active AS. Patients entered the model with a BASDAI of 4 or more and received infliximab, etanercept or usual care. In each treatment option, two disease states were distinguished. These contrasted patients with active disease (BASDAI ≥ 4) with patients with low disease activity (BASDAI <4). Response to treatment was defined as achieving a state of low disease activity (BASDAI <4). Response could be followed at any time during treatment by a relapse to a BASDAI score of more than 4 or by major toxicity. Patients not responding or relapsing stopped receiving TNF-alpha inhibitors and continued usual care. Major toxicity was followed by treatment of the toxicity and a 3-month cessation of the TNF-alpha inhibitors while continuing the beneficial clinical effect of TNF-alpha inhibition. After the toxicity had been treated, patients could either continue with TNF-alpha inhibitors or discontinue them, followed by relapse to high
disease activity and continuing usual care. All patients entering the model were screened for tuberculosis.

**Outcomes assessed in the review**
The outcomes estimated from the literature were the rates of response, relapse, major toxicity, response after relapse or toxicity-related withdrawal, and discontinuation after major toxicity. Utility values were associated with the health states BASDAI \( \geq 4 \) and BASDAI <4.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature was undertaken to identify the primary estimates. Data on short-term clinical effectiveness and toxicity for the anti-TNF inhibitors came from two randomised clinical trials. Short-term effectiveness and toxicity of usual care was also obtained from the placebo arm of these two clinical trials. On the other hand, long-term effectiveness and toxicity were estimated from open studies (anti-TNF inhibitors) and a 4-year observational study of a Dutch cohort of patients with AS (usual care). The utility values were obtained from a 2-year longitudinal study with 130 Dutch patients with AS. These patients completed the Euro-Qol 5-D questionnaire every 6 months and the utility values for the main health states were obtained using time-averaged values.

**Sources searched to identify primary studies**
Not reported.

**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**
Twelve primary studies provided the clinical evidence.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
The characteristics of the patients included in the two clinical trials and in the Dutch observational study were reported, but no statistical analysis was performed to address the issue of homogeneity of the primary studies. The authors emphasised that no head-to-head comparisons between etanercept and infliximab were available.

**Results of the review**
The probability of response in the first 3 months was 0.16 (range: 0.06 to 0.26) with usual care, 0.71 (range: 0.45 to 0.88) with etanercept, and 0.62 (range: 0.45 to 0.76) with infliximab.

The probability of response with usual care was 0.02 (range: 0.01 to 0.04) in the first year after the first cycle and 0.01 (range: 0.005 to 0.02) in the second to fifth years after the first cycle.

The probability of relapse to BASDAI \( \geq 4 \) with etanercept was 0.26 (range: 0.08 to 0.44) in the first year after the first cycle, 0.08 (range: 0.005 to 0.15) in the second year, and 0.02 (range: 0.01 to 0.04) in the third to fifth years after the first cycle.
The probability of relapse to BASDAI \( \geq 4 \) with infliximab was 0.16 (range: 0.02 to 0.31) in the first year after the first cycle, 0.08 (range: 0.005 to 0.15) in the second year, and 0.02 (range: 0.01 to 0.04) in the third to fifth years after the first cycle.

The probability of major toxicity with etanercept was 0 in the first 3 months, 0.08 (range: 0.03 to 0.18) in the first year after the first cycle, and 0.04 (range: 0.015 to 0.09) in the second to fifth years after the first cycle.

The probability of major toxicity with infliximab was 0.12 (range: 0.01 to 0.23) in the first 3 months, 0.13 (range: 0.05 to 0.26) in the first year after the first cycle, and 0.04 (range: 0.015 to 0.09) in the second to fifth years after the first cycle.

The rate of response after relapse or toxicity related withdrawal with etanercept and infliximab was 0.05 (range: 0.025 to 0.1) in the first cycle and in the first year after the first cycle, and 0 in the second to fifth years after the first cycle.

The rate of discontinuation due to major toxicity was 0.5 (range: 0 to 1) with both medications.

The utility value was 0.59 (range: 0.55 to 0.63) for a state of BASDAI \( \geq 4 \), and 0.76 (range: 0.74 to 0.79) for a state of BASDAI <4.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
It was assumed that tuberculosis screening would prevent occurrence of active tuberculosis during treatment.

Rheumatologists who were experienced in the treatment of patients with AS using TNF-alpha inhibitors stated that there was no difference between etanercept and infliximab in the probabilities for relapse and toxicity beyond the duration of observational trials.

In the case of toxicity, the utility was reduced by 50%.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated by combining survival data and utility adjustments for different conditions considered in the decision model. The utility values were obtained from a cohort of Dutch patients using the Euro-Qol 5-D. An annual discount rate of 4% was applied. The number of months in the BASDAI <4 state over 5 years was also reported.

**Direct costs**
The analysis of the costs was carried out from a societal perspective. The direct medical costs included were for etanercept, infliximab, screening and prophylaxis for tuberculosis (including a skin test, chest X-ray, and further diagnosis and treatment, if required), treatment of toxicity, and treatment of AS in different health states (BASDAI <4 or BASDAI \( \geq 4 \)). The unit costs were not presented separately from the quantities of resources used for most items. The costs of disease came from a longitudinal study of 130 Dutch patients. The sources of the other costs and resource consumption were not explicitly stated. Discounting was relevant, as the costs were incurred during a 5-year timeframe, and an annual rate of 4% was applied. The costs were inflated to 2002 values using consumer price indices.

**Statistical analysis of costs**
The costs were presented as mean values with bootstrapped 95% confidence intervals.

**Indirect Costs**
The indirect costs (i.e. productivity losses due to AS) were included since a societal perspective was adopted. The estimation of the indirect costs was based on the friction cost method. Details of the calculation of these costs were not reported. The price year was 2002 and an annual discount rate of 4% was applied, as in the analysis of the direct costs.

Currency
Euros (EUR).

Sensitivity analysis
Univariate sensitivity analyses were carried out to assess the robustness of the cost-utility ratios to variations in model inputs, such as:

the costs (indirect costs were either estimated using the human capital approach or were excluded),

the dose of infliximab (reduced to 3 mg/kg every 8 weeks after loading, while assuming the same efficacy),

the time horizon (reduced to 2 years), and

the placebo response in patients receiving usual care (it was assumed no change in health status).

Further, several best-case analyses were performed by biasing the model in favour of TNF-alpha inhibitors. Finally, a threshold analysis was carried out to estimate the drug acquisition cost for which the cost-utility would be acceptable to Dutch society (EUR 18,000 per QALY).

Estimated benefits used in the economic analysis
Over a 5-year timeframe, the expected QALYs were 2.89 with usual care, 3.16 with etanercept, and 3.11 with infliximab.

The estimated months in BASDAI <4 were 10.7 with usual care, 31.4 with etanercept, and 28.4 with infliximab.

Cost results
The expected 5-year total costs were EUR 21,261 with usual care, EUR 52,137 with etanercept, and EUR 62,047 with infliximab.

After the exclusion of indirect costs, the total direct costs were EUR 19,425 with usual care, EUR 49,555 with etanercept, and EUR 59,574 with infliximab.

Synthesis of costs and benefits
Incremental cost-utility ratios and cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative strategies.

The incremental cost per QALY gained over usual care was EUR 118,022 with etanercept and EUR 189,564 with infliximab.

The incremental cost per extra month with low disease activity in comparison with usual care was EUR 1,492 with etanercept and EUR 2,307 with infliximab.

The sensitivity analysis showed that the cost-utility ratio approached the threshold set by Dutch society only when the drug acquisition costs were a quarter of the price for etanercept and one fifth of the price for infliximab. Variations in other model inputs did not substantially alter the results of the base-case analysis. However, a high variability was found in the incremental cost per QALY of the anti-TNF inhibitors versus usual care (range: EUR 42,443 to EUR 189,564).
Authors' conclusions
Etanercept and infliximab improved clinical outcomes in patients with ankylosing spondylitis (AS), but the high drug acquisition cost of both drugs limits the cost-effectiveness of the two treatments in the Dutch setting. Only substantial reductions in drug prices could make etanercept and infliximab cost-effective.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear since the two new treatments were compared with the conventional approach for patients with AS. The authors stated that a comparison between etanercept and infliximab was beyond the objectives of the study, owing to the lack of head-to-head drug comparisons. You should decide whether these are valid interventions in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published sources. However, it was not clear whether the studies were identified from a review of the literature; no information on the conduct and method of a review was provided. Some details of the clinical trials used to derive effectiveness and toxicity data in the short term were given. The use of clinical trials might enhance the internal validity of the study. However, the long-term data were based on observational studies, experts' opinions, and assumptions, and this might have introduced uncertainty into the analysis. The issue of homogeneity across the primary studies was not addressed. The impact of changing clinical data on the results of the study was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The choice of QALYs as the summary benefit measure was appropriate since QALYs capture the impact of the intervention on both quality of life and survival. Quality of life is an important dimension of health for patients with AS, and QALYs can be compared with the benefits of other health care interventions. The utility values were obtained from a cohort of Dutch patients, which appears to have been a strength of the study. Discounting was applied. A disease-specific benefit measure was also used, although this might only be comparable with the benefits of similar interventions.

Validity of estimate of costs
The analysis of the costs was carried out from a societal perspective, which was appropriate since productivity losses associated with AS were relevant for the patients considered in the analysis. The approach used to assess the indirect costs was reported and an alternative method was also used. Some costs were obtained from an observational study with Dutch patients, but the sources of other categories of costs were not clear. The unit costs and resource quantities were not given, which limits the possibility of replicating the cost analysis in other settings. The authors stated that confidence intervals for costs were calculated, but only point estimates were reported. The price year was reported, which will assist with reflation exercises in other time periods. The authors stated that, despite the substantial work disability for patients with AS, the model showed little impact of the indirect costs on total costs because of the approach used to calculate productivity losses.

Other issues
The authors reported the results from two published cost-utility analyses of treatments for AS. Differences observed between these and the findings of the current study were discussed. The issue of the generalisability of the study results to other settings was not explicitly addressed, but several sensitivity analyses were performed, which enhances the external validity of the study. The authors noted some limitations of the decision model and the drawback of mixing data from different sources (with potentially different patient populations). However, it was noted that even when best-case scenarios were considered, the cost-utility ratio of both TNF-alpha inhibitors remained high. Further, the authors pointed out that the gains in utility associated with TNF-alpha inhibitors might have been underestimated given the characteristics of the patients included in the observational study (less severe than those in the clinical trials). Finally, the use of a 5-year time horizon might not have taken the longer term benefits of the anti-TNF treatment into account.
Implications of the study

The study results do not support the use of etanercept and infliximab for the treatment of patients with AS. The authors made some recommendations for future research, based on a better definition of outcome measures, the use of utility data derived directly from observational studies, and the use of long-term data.

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Other publications of related interest


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