Comparison of the cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in the United Kingdom based on two different clinical trials

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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 the treatment of ankylosing spondylitis (AS) with infliximab (5 mg/kg every 6 weeks) compared with standard treatment. Standard treatment was defined as no treatment (placebo, as used in the clinical trials on which the study based the effectiveness estimates).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with active AS, according to the ASAS criteria, for several years.

Setting
The setting was outpatients. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were collected from two randomised controlled trials published in 2002 and 2005. Average annual disease progression was estimated from two epidemiological surveys conducted in 1992 and 2002 (published in 1998 and 2004). The cost and utility data were derived from a survey conducted in 2004. The price year was 2005.

Source of effectiveness data
The clinical data included the effectiveness of infliximab treatment in improving Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores; the authors did not report these improvements. The average annual disease progression in the model was expressed by changes in BASFI. The same rate of progression was used in the model for all patients, regardless of age or level of disability. Standardised UK population mortality was incorporated.

Modelling
A decision tree representing the double-blind periods of the trials with a subsequent Markov model to estimate disease progression, was developed. A lifetime horizon was used. The health states and cycle length were presented in full, along with a number of modelling assumptions which were fully justified. The estimates were based on first-order Monte Carlo simulations (10,000 simulations).
**Sources searched to identify primary studies**
The clinical effectiveness data were derived from two randomised control trials, the ASSERT trial and the Braun trial (VanderHeijde et al. 2005 and Braun et al. 2002, see Other Publications of Related Interest- below for bibliographic details). Disease progression was estimated from two epidemiological surveys conducted at the University of Bath. In the analysis, three assumptions were used for the progression of functional disability on treatment. The assumptions were that functional disability does not progress while on treatment, a 50% reduced progression while on treatment, and no effect of treatment on progression.

**Methods used to judge relevance and validity, and for extracting data**
The authors did not report how data used in the model were identified or selected for inclusion. The methods of reviewing the literature were not reported and, given this, it is unlikely that a systematic approach was taken.

**Measure of benefits used in the economic analysis**
The summary measure of benefit used was the quality-adjusted life-years (QALYs) gained. The utility data were collected in a cross-sectional retrospective study of patients with AS, conducted at the University of Bath (Kobelt et al. 2004, see Other Publications of Related Interest- below for bibliographic details), using the EuroQol (EQ-5D) questionnaire. The authors reported that 1,413 patients participated in the study. The utility values were assigned with regression analysis and bootstrapping from the full distribution of values. The benefits were discounted at a rate of 3.5%.

**Direct costs**
The direct costs included in the analysis from the NHS and PSS perspective were those of the health services. Community services and patients costs were also included when the perspective of the analysis was societal. The direct costs included were for health care and community services use, out-of-pocket expenses and informal care related to AS. These costs were derived from the same survey that provided utility data. The treatment costs included the cost of a 100-mg vial of infliximab (based on 5 mg/kg on weeks 0, 2 and 6, and then every 6 weeks), and an outpatient visit for each infusion. The cost of adverse events possibly related to treatment was estimated from the Braun trial. Given the highly skewed costs the cost components were estimated using a two-part regression model, with BASDAI, BASFI, age and gender as explanatory variables. The costs were discounted at a rate of 3.5%. The resources and unit costs were not reported separately. The price year was 2005. The costs were adjusted using the Consumer Price Index.

**Statistical analysis of costs**
No statistical analysis of the costs was presented as the objective was to produce cost-utility estimates.

**Indirect Costs**
The authors reported that they had included data on work capacity that were collected in a survey conducted in 2004 on which the costs and utilities were based. The costs were discounted at a rate of 3.5%. The resource quantities and the unit costs were not reported separately. The price year was 2005. The costs were adjusted using the Consumer Price Index.

**Currency**
UK pounds sterling ().
acceptability curves using second-order Monte-Carlo simulations (10,000 for each case), varying the costs, utilities, progression rates and BASFI values.

Estimated benefits used in the economic analysis
The QALYs gained per patient with each treatment were not reported.

Under the assumption of no progression while on treatment for infliximab patients, the QALYs gained from using infliximab were 1.28 in the Braun trial for both perspectives and 1.27 in the ASSERT trial for both perspectives.

Under the assumption of 50% progression while on treatment for infliximab patients, the QALYs gained were 1.01 in both trials.

Under the assumption of the same progression in both groups, the QALYs gained ranged from 0.8 to 0.88, depending on the trial and perspective.

Cost results
The cost per patient for each treatment was not reported.

Under the assumption of no progression while on treatment for infliximab patients, the incremental cost from the societal perspective was -16,872 in the Braun trial and -15,927 in the ASSERT trial. The incremental costs from the NHS perspective were 36,378 (Braun trial) and 33,920 (ASSERT trial), respectively.

Under the assumption of 50% progression while on treatment for infliximab patients, the incremental cost from the societal perspective ranged from -3,975 to -5,233. The incremental cost from the NHS perspective ranged from 33,756 to 34,408.

Under the assumption of the same progression in both groups, the incremental cost from the societal perspective ranged from 12,156 to 10,540. The incremental cost from the NHS perspective ranged from 39,336 to 39,242.

When using the two-part regression model, the authors reported that costs were driven by the BASFI and BASDAI, with age having a small non significant effect.

Synthesis of costs and benefits
The estimated benefits and costs were combined in the form of incremental cost-effectiveness ratios. The discount rate used for the costs and benefits was 3.5% and the price year was 2005.

From a societal perspective, treatment with infliximab dominated in both trials in the first two scenarios. This means that infliximab was both cheaper and more effective than the comparator treatment. For this reason, the costs and benefits were not combined in the form of an incremental cost-effectiveness ratio.

Under the assumption that treatment has no effect on disease progression, the cost per QALY gained was 15,045 per QALY for the Braun trial and 11,937 per QALY for the ASSERT trial.

From the NHS perspective and under the assumption that most favoured infliximab (i.e. no progression while on treatment), the incremental cost-effectiveness ratio ranged from 26,751 per QALY to 28,332 per QALY.

The ratio increased as the assumption was changed to ones that did not favour infliximab as much. For the assumption of same progression in both groups, the ratio ranged from 46,167 per QALY to 49,417 per QALY.

It was reported that the results were most sensitive to the treatment costs, the dosing regimen adopted, the discontinuation rate, assumptions concerning disease progression while on treatment and the time horizon. The stochastic analysis indicated that there was relatively little uncertainty around the cost-effectiveness results obtained from the two trials. For the base-case scenario (disease activity controlled and functional capacity stable while on drug),
there was an 80% probability that the cost per QALY would fall below the threshold of 30,000 for the NHS and PSS perspective. For the societal perspective, 100% of the estimates were cost-saving for the base-case scenario.

Authors' conclusions
"The two clinical trials yield the same cost-effectiveness results and the cost per quality-adjusted life-year (QALY) gained with treatment was found to be in the acceptable range."

CRD COMMENTARY - Selection of comparators
Although no explicit justification was provided for the comparator used (i.e. placebo), this was the comparator used in the two clinical trials on which the study based its effectiveness estimates. This allowed the active value of the treatment to be evaluated but did not include an active agent as an alternative. You should decide if a "no treatment" strategy represents a valid comparator in your own setting

Validity of estimate of measure of effectiveness
The effectiveness parameters were derived from published research, namely two randomised clinical trials. The information on these trials was limited, making it difficult to comment on the quality of the effectiveness estimates. Adverse events possibly related to treatment were estimated from one of the trials. Assumptions about treatment beyond the trials were based on open extensions from the trials and treatment guidelines produced by the British Society for Rheumatology. No synthesis was conducted. In addition, the authors did not report any search methods or inclusion criteria, or provide any justification for their selection of the estimates. It is therefore possible that the data from the available studies were used selectively.

Validity of estimate of measure of benefit
The summary measure of benefit was utility gain in the form of QALYs gained. The derivation of the utilities was adequately described. This outcome measure fully captures the health benefits of the intervention and allows for comparisons with other technologies. The authors acknowledged that the EQ-5D was very widely used in studies of rheumatology and had been shown to be very sensitive to changes in function and inflammation. The QALYs gained were reported disaggregated from the costs in the form of incremental QALYs gained. The benefits were appropriately discounted.

Validity of estimate of costs
The analysis of the costs was performed from two different perspectives (i.e. the NHS and PSS perspective and the societal perspective). All the categories of costs and costs relevant to both perspectives appear to have been included in the analysis. Resource use and cost data were derived from published sources. The costs were appropriately adjusted and discounted. Uncertainty in the cost data was only evaluated jointly with effectiveness data through cost-effectiveness acceptability curves. The costs and the quantities were not reported separately. In fact, only the incremental costs of infliximab over and above no treatment were presented.

Other issues
The authors noted that bootstrapping the utility and cost regression coefficients from an observational study while controlling for age, gender, BASDAI and BASFI allowed the clinical and observational data to be combined, despite demographic differences in the samples and accounting for advancing age. The authors evaluated the impact of varying the dosing regimen, which was known to vary by setting, on the incremental cost-effectiveness ratio. Effective treatment could be provided with a lower dose and more individualised dosing schedules. It was noted that despite exploring the effect of these reduced regimens on the cost-effectiveness, the absence of patient-level data made it impossible to compare effectiveness. Hence, one limitation noted was the assumption that effectiveness, for this sensitivity analysis, would be the same in the Braun and ASSERT trial. Another limitation noted was the small size of the sample in the extension phase and the need to confirm withdrawal findings in clinical practice. The authors justified the use of a societal perspective for the main analysis as the social costs of the disease were substantially higher than NHS costs alone.
The authors compared their findings with another cost-effectiveness study, which suggested that the results were very different. Reasons for these differences were proposed, such as differences in the time horizon, analysis of the effect of treatment, and the measurement of costs and utilities. The results do not appear to have been presented selectively. The study enrolled patients with AS who were given or not given treatment, and this was reflected in the authors’ conclusions.

**Implications of the study**

The authors noted that their analysis shows the importance of selecting those patients for treatment who are likely to benefit most and of selecting the appropriate regimen, in order to use resources in a cost-effective way. A call for the application of the British Society for Rheumatology guidelines was explicitly made. The application of these guidelines would help biological drugs such as infliximab to be cost-effective. No further research was explicitly identified, although the discussion highlighted some areas where limitations are present, implying the need for greater information.

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**Other publications of related interest**

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**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adult; Antibodies, Monoclonal /economics /therapeutic use; Antirheumatic Agents /economics /therapeutic use; Clinical Trials as Topic; Computer Simulation; Cost-Benefit Analysis; Disease Progression; Female; Great Britain; Humans; Infliximab; Male; Models, Econometric; Quality-Adjusted Life Years; Reproducibility of Results; Spondylitis, Ankylosing /drug therapy; State Medicine /economics