The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab
(Remicade)

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 use of infliximab, 5 mg/kg every 6 weeks with a loading infusion after 2 weeks, in the treatment of ankylosing spondylitis (AS).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients suffering from AS.

Setting
The setting of the clinical study, although not explicitly reported, appears to have been secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were gathered from studies published from 1997 to 2003. The resource use data were obtained from public sources available on the Internet, published in 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a review of the literature.

Modelling
Two models were developed to estimate the cost-effectiveness. The main, short-term model tracked the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores for every patient in the trial over 2-year period. The long-term model used a Markov model to track the change in BASDAI and BASFI scores over a 3-year period. The BASDAI and BASFI scores depended on three states in the Markov model, specifically, on treatment, off treatment and dead.

For both models, the costs were linked to BASDAI and BASFI scores using a 2-step regression model developed from survey and trial data. The utilities were calculated for discrete levels of BASDAI and BASFI scores using survey data.

Outcomes assessed in the review
Clinical trial and survey data were used to derive the change in BASFI and BASDAI scores over time.

**Study designs and other criteria for inclusion in the review**
There was no systematic review of the literature, so there were no inclusion criteria. Three datasets were used. The first was a randomised double-blind, placebo-controlled 12-week trial with a one-year open extension, which enrolled 70 patients with confirmed AS. The second was a cohort study of 700 patients followed in clinical practice for up to 9 years. The third was a cross-sectional survey of 2,300 patients who had participated in a population survey carried out between 1992 and 1994.

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

**Criteria used to ensure the validity of primary studies**
Not relevant.

**Methods used to judge relevance and validity, and for extracting data**
Not relevant.

**Number of primary studies included**
Not relevant.

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

**Investigation of differences between primary studies**
Not relevant.

**Results of the review**
The review of clinical datasets revealed that, at baseline, the mean BASDAI score was 6.3 (standard deviation, SD=1.4) in the placebo group versus 6.5 (SD=1.1) in the infliximab group. The BASFI scores were 5.1 (SD=2.2) and 5.5 (SD=1.8), respectively. At the end of 12 weeks, the BASDAI score was 5.0 (SD=0.4) in the placebo group versus 3.4 (SD=0.4) in the infliximab group, and the BASFI scores were 5.7 (SD=0.5) and 3.2 (SD=0.4), respectively.

At the end of 54 weeks, the mean BASDAI score and the mean BASFI score reached the same value 2.8 (SD=0.4) for the infliximab group.

The mean duration of duration was 14.9 years (SD=9.3) in the placebo group versus 16.4 years (SD=8.3) in the infliximab group.

The review of the cohort study and the observation survey revealed that the mean BASDAI score was 4.2 (SD=2.3) and the mean BASFI score was 4.4 (SD=2.8).

The mean duration of disease was 30.2 years (SD=11.7).

The article also reported the demographic parameters and the details of these parameters on the basis of five intervals of BASDAI and BASFI scores.
**Measure of benefits used in the economic analysis**

The summary measure of benefits used was the quality-adjusted life-years (QALYs). Average QALYs were calculated for discrete BASFI and BASDAI scores, using the EQ-5D health state system. The QALYs were discounted at an annual rate of 1.5%.

**Direct costs**

The direct costs included in the economic evaluation were for hospitalisation, outpatient visits, community care, drugs and over-the-counter medication. The resource consumption data were taken from a questionnaire sent to a cohort of patients at the University of Bath. The unit costs for all of these were derived from the review of public sources available on the Internet. A 2-step regression model was used to link costs with the BASDAI and BASFI scores. An annual discount rate of 6% was applied, as required for an economic analysis in the UK. The unit costs were reported separately from the quantities of resources used for significant cost items. The price year was 2002.

**Statistical analysis of costs**

The authors presented the mean annual cost per patient with SD, although they did not report the type of statistical tests used.

**Indirect Costs**

The indirect costs were for short-term leave, reductions in working time due to AS and early retirement. They were derived from a questionnaire completed by patients at the University of Bath. The loss of production was estimated using the human capital approach, as recommended by the National Institute for Clinical Excellence (NICE) in the UK. An annual discount rate of 6% was also applied to the indirect costs.

**Currency**

UK pounds sterling (£).

**Sensitivity analysis**

Univariate sensitivity analyses were conducted to investigate the uncertainty in the estimates used in the decision models. In the main model, the key parameters varied were the discount rates of effect and cost, the indirect cost, the cost of infliximab, and the timeframe of treatment. Besides the first three items above, the parameters varied in the long-term model included the annual progression on BASFI and the annual drop-out rate.

**Estimated benefits used in the economic analysis**

In the main model, the incremental QALYs gained over 2 years were 0.175 when a 1.5% discount rate was applied. The long-term model revealed that the incremental QALYs gained over 30 years were 2.62 when a 1.5% discount rate and a 10% drop-out rate were applied.

**Cost results**

In the 2-year model, the incremental cost of infliximab over standard treatment was 6,214 (discounted by 6%).

In the long-term model over 30 years, the total incremental cost with infliximab over standard treatment was 25,200.

**Synthesis of costs and benefits**

In the baseline case, the incremental cost per QALY gained was 35,400 for the first year of treatment in the main model, and 9,600 in the long-term model.

In the short-term model, the sensitivity analyses showed that the incremental cost per QALY gained was reduced to
32,800 if infliximab treatment was extended from 1 to 2 years. When infliximab infusions were given every 8 weeks instead of every 6 weeks, the value was reduced to 17,300. In the long-term model, the incremental costs per QALY gained were 4,900 at a 3% discount rate (effect and costs), 2,800 with no progression for patients on treatment, and 700 with a 15% drop-out rate. Other results of the sensitivity analyses were reported in the original paper.

Authors' conclusions
The treatment of ankylosing spondylitis (AS) with infliximab was cost-effective from a societal perspective, with a cost per quality-adjusted life-year (QALY) gained in the vicinity of 30,000 to 40,000 in the short term and potentially below 10,000 in the long term.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Infliximab treatment of AS was compared with conventional treatment. Conventional treatment was not specified. You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were not derived from a review of the literature but from specially selected studies. Since it appears that a systematic review of the clinical literature was not performed, it was not clear whether the best available data were included. There was a lot of uncertainty in the effectiveness data for the long-term model. However, sources searched and other methodological details were not given.

Validity of estimate of measure of benefit
The use of QALYs as the benefit measure was appropriate for assessing the impact of the health intervention. They also enable comparisons with the results of other studies, or with the treatments in other diseases. Discounting of the benefits was carried out according to NICE guidelines.

Validity of estimate of costs
The cost analysis was conducted from a societal perspective. It appears that all the relevant categories of costs have been included in the study. The unit costs and the resource quantities were analysed separately. The unit cost data were obtained from public sources on the Internet, while resource use was based on a survey. The price year was reported, which simplifies reflation exercises in other settings.

Other issues
The authors compared the results of their analysis with published studies investigating other medical treatments for different diseases. This study adopted a societal perspective because the indirect cost related to productivity accounted for a high proportion of the total costs. It was noticed that the benefits of treatment might have been underestimated, and the authors provided explanations for this. The issue of the generalisability of the cost and effectiveness results to other settings was addressed by the performance of sensitivity analyses. The authors' conclusions reflected the scope of the analysis.

Implications of the study
The threshold level recommended by NICE for treatment indicated that the treatment of AS with infliximab was cost-effective from a societal perspective. The authors suggested that more data for larger groups of patients is required to confirm the findings.

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