Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis
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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 use of infliximab, an anti-tumour necrosis factor A drug, for the treatment of rheumatoid arthritis (RA).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients suffering from active and refractory RA. Active RA was defined as a combination of synovitis (at least 6 swollen or tender joints) and other symptoms (such as morning stiffness).

Setting
The setting of the clinical study, although not explicitly reported, appears to have been that of a hospital (rheumatology ward). The economic study was performed in Boston (MA), USA.

Dates to which data relate
The effectiveness and resource use data were gathered from studies published from 1999 to 2001. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from published studies and the authors' assumptions.

Modelling
A deterministic Markov model was constructed in order to estimate the lifetime costs and quality-adjusted lifetime expectancy for infliximab plus MTX versus MTX alone. The Markov model consisted of 21 health states, based on a combination of five treatments and four disability levels (plus death). The five treatments included were infliximab plus MTX, MTX alone, disease-modifying antirheumatic drugs (DMARDs), MTX plus another DMARD, and non-steroidal anti-inflammatory drugs (NSAIDs). The disability levels were assessed according to the Health Assessment Questionnaire (HAQ), which is a standard clinical measure in RA ranging from 0 (no impairment) to 3 (advanced impairment). The four disability levels were HAQ equal to 0, HAQ from 0.1 to 1, HAQ from 1.1 to 2, and HAQ from 2.1 to 3. The cycle length was 6 months and the time horizon was lifetime.

Outcomes assessed in the review
The primary outcomes assessed from the literature were the general health-related quality of life associated with each
treatment included in the model and with each disability level, and the transition probabilities from one state to another.

**Study designs and other criteria for inclusion in the review**
Clinical outcomes for infliximab plus MTX versus MTX alone in the first 54 weeks were taken from the ATTRACT trial. This was a randomised controlled trial that enrolled 428 patients with refractory and active RA. Results beyond the 54 weeks were estimated using the ARAMIS cohort, which prospectively enrolled 4,258 patients with RA, followed for 17,085 patient-years.

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

**Criteria used to ensure the validity of primary studies**
The authors did not state any criteria used to ensure the validity of the primary studies. However, the use of a randomised controlled trial (with a large sample size) ensures the internal validity of the study.

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

**Number of primary studies included**
The effectiveness evidence was obtained from two primary studies.

**Methods of combining primary studies**
The two primary studies used to populate the model were not combined. The ATTRACT trial was used to obtain clinical data for the first 54 weeks, while the ARAMIS cohort was used to extrapolate the results over a lifetime period.

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

**Results of the review**
After 54 weeks of treatment, the general health-related quality of life was 0.509 (+/- 0.199) for patients receiving MTX alone versus 0.621 (+/- 0.202) for those receiving infliximab plus MTX.

The general health-related quality of life associated with the health states in the Markov model varied on the basis of the treatment received and the level of disability.

For HAQ of 0, the utility values ranged from 0.836 (+/- 0.177) with MTX plus DMARD to 0.891 (+/- 0.138) with NSAIDs.

For HAQ of 0.1 to 1, the utilities ranged from 0.714 (+/- 0.192) with MTX plus DMARD to 0.738 (+/- 0.183) with NSAIDs.

For HAQ of 1.1 to 2, the utilities ranged from 0.539 (+/- 0.190) with NSAIDs to 0.574 (+/- 0.186) with MTX.

For HAQ of 2.1 to 3, the health-related quality of life ranged from 0.400 (+/- 0.214) with NSAIDs to 0.434 (+/- 0.227) with MTX alone.

A 12x16 matrix of transition probabilities, based on the treatment received and disability levels, was also reported. A high proportion of patients (varying from approximately 60 to 95%) who started from a disability level and a type of
Methods used to derive estimates of effectiveness
The mortality rate for RA patients in different disability levels was derived from the authors’ assumption.

Estimates of effectiveness and key assumptions
The mortality rate was 1.77-fold greater for each increase in disability level, compared with an age and gender-matched general population.

Measure of benefits used in the economic analysis
The summary measure of benefits used in the economic analysis was the quality-adjusted life-years (QALYs). Both the ARAMIS database and the ATTRACT trial included the patients’ self-reported assessments of their health on a visual analogue scale (VAS). The QALYs were calculated using the utilities obtained from the VAS and the mortality rates assumed by the authors.

Direct costs
A 3% annual discount rate was applied, which was appropriate given the long time horizon used in the decision model. The quantities of resources used and the unit costs were not reported separately. The quantity/cost boundary adopted was that of society. The direct costs included were for drugs, hospitalisations (including rehabilitation), emergency room visits, outpatient surgeries, personnel, laboratory tests and home care (including nursing homes). Resource use was derived from the data obtained from patients in the ATTRACT trial for the first year and from patients in the ARAMIS cohort for subsequent years. The source of the unit costs was not explicitly reported. The studies from which the resource use data were gathered were published between 1999 and 2001. The costs were adjusted to 1998 using the medical care component of the US Consumer Price Index.

Statistical analysis of costs
The authors reported the 95% confidence interval around the mean cost for each health state included in the model. The total costs for the two treatments compared were treated deterministically.

Indirect Costs
A 3% annual discount rate was also applied to the indirect costs. The indirect costs for the first year were obtained from a subgroup of patients in the ATTRACT trial. The indirect costs in subsequent years were assumed to be three times the direct costs in the base-case, on the basis of published studies. No further details were reported.

Currency
US dollars ($).

Sensitivity analysis
Several univariate sensitivity analyses were carried out to test the robustness of the results in the base-case. The key parameters varied were the discount rate, indirect costs, cost of infliximab, cost of RA care, gender and age of the patients, probability of disease progression, mortality rate and quality of life with infliximab.

Estimated benefits used in the economic analysis
The incremental QALYs gained in a lifetime period with infliximab plus MTX versus MTX alone were 0.34 when no discount rate was applied (13.33 versus 12.99) and 0.29 when a 3% discount rate was applied (9.40 versus 9.11).
**Cost results**
The incremental lifetime direct costs with infliximab plus MTX versus MTX alone were $9,000 ($125,900 versus 116,900) when no discount rate was applied, and $8,900 ($93,000 versus $84,100) when a 3% discount rate was applied.

When the indirect costs were also considered the incremental cost of infliximab decreased. The incremental costs ranged from $2,900 without discounting to $2,600 with a 3% discount rate.

**Synthesis of costs and benefits**
In the base-case, the incremental cost of adding infliximab to MTX was $26,800 per QALY gained without discounting, and $30,500 per QALY gained at a 3% discount rate, in a lifetime period.

The results of the sensitivity analyses did not substantially alter the results of the base-case, and the incremental cost-effectiveness ratios calculated always fell below $50,000.

The parameter that caused the highest variability in the incremental cost-effectiveness of infliximab was the cost of the drug itself.

In general, the inclusion of the indirect costs, or the assumption of higher costs of RA care reduced the incremental cost-effectiveness ratio for infliximab.

Infliximab, in reducing the progression of RA, is likely to reduce the future indirect and direct costs of RA. The greater these future costs, the larger the cost that is offset with infliximab. Hence, the more cost-effective the drug.

**Authors’ conclusions**
Infliximab can be considered a cost-effective strategy for patients suffering from refractory and active rheumatoid arthritis (RA). It showed a cost-effectiveness ratio below $50,000, which is a well-accepted threshold for medical therapies for chronic diseases.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Infliximab (a new anti-tumour necrosis factor A drug) plus MTX was compared with MTX alone (considered to be the placebo). You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from published studies, although no review of the literature was performed. The studies included were randomised controlled trials, which assures high internal validity, and a large sample cohort database appropriate to the US context. The disability level for determining the health states in the Markov model was based on the HAQ, which is a common validated instrument in RA.

**Validity of estimate of measure of benefit**
The use of QALYs as the measure of benefits guarantees the comparability of the results of this analysis with other studies performed on RA, or on other diseases, and in other areas. The utilities were estimated using the VAS score. These are usually different from the utilities obtained in the traditional sense (with time trade-off or standard gamble). However, the estimation of the QALYs gained depends on changes in VAS score, and there should be no bias resulting from the approach used.

**Validity of estimate of costs**
A societal perspective was adopted in the analysis and the authors included both the direct medical costs and indirect...
costs. Several sensitivity analyses were performed to test the robustness of the analysis. Also, to address the issue of transferability of the results. However, only limited details about resource use and the unit costs were given. The resource use data were collected from the patients included in the ATTRACT trial and ARAMIS.

Other issues
The authors compared the cost-effectiveness results of their analysis with published studies investigating other medical therapies for different diseases. However, they did not compare their results with results obtained for other RA drugs. The societal perspective adopted in this study was particularly important given the high proportion of productivity costs that involves a chronic disease such as RA. The fact that the authors defined the health states, not only in terms of disability levels but also the treatment received, is probably due to the fact that it was felt that the HAQ does not fully capture all clinical characteristics. However, the authors did not explicitly explain this concept.

Implications of the study
The authors state that longer follow-up of the infliximab clinical studies must be performed to confirm the results of their analysis.

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Other publications of related interest


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