The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study
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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 addition of infliximab (Remicade) to methotrexate for the treatment of patients with rheumatoid arthritis (RA). The standard dose prescribed in clinical practice was 3 mg/kg every 8 weeks with an initial loading dose at weeks 0, 2 and 6 (i.e. 24 mg/kg per year). Two treatment durations, 1 year and 2 years, were considered.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with RA.

Setting
The setting was secondary care. The economic study was carried out in the UK and Sweden.

Dates to which data relate
The effectiveness data and most resource use data were derived from studies published between 1990 and 2002. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to assess the 10-year cost-effectiveness of infliximab added to methotrexate in comparison with methotrexate alone for the treatment of a hypothetical cohort of patients with RA. Patients could receive infliximab plus methotrexate for 1 or 2 years or methotrexate alone. At the end of this period, patients in both arms received the same treatments (mainly other DMARDs). The structure of the model was presented graphically. The cycle length was annual. The model had 6 health states based on functional disability (state 1 represented least disability and state 6 worst disability), measured using the Health Assessment Questionnaire (HAQ), and one state for death. After each cycle, the model redistributed patients in the different states, depending on whether their HAQ scores had improved, remained stable or worsened during that cycle, or whether the patient had died during the cycle.
Outcomes assessed in the review
The outcomes assessed from the literature were treatment effectiveness, epidemiological characteristics of the disease, utility values associated with specific health states, and mortality.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively rather than through a systematic review of the literature. The data on treatment effectiveness came from a multi-centre, double-blind, randomised clinical trial (ATTRACT trial) that enrolled 428 RA patients who could receive infliximab (at different dosages) plus methotrexate or methotrexate alone. The long-term pattern of disease in the two countries was estimated from two cohort studies. In the Lund cohort in Sweden, 183 patients were followed for up to 16 years. In the Early RA Study (ERAS) in the UK, 1,473 patients were followed for up to 15 years. Mortality data were estimated from normal age- and gender-adjusted mortality statistics in each country. The utility data were obtained from the Lund and ERAS cohorts using patients’ preferences based on the EuroQol.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The primary sources used to derive the clinical data were valid: a clinical trial was used for short-term effectiveness data, while two long-term epidemiological studies were used to extrapolate these data.

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

Number of primary studies included
Eight primary studies provided the clinical data.

Methods of combining primary studies
The primary estimates were not combined as each source provided a discrete series of clinical data. Transition probabilities between states were estimated using an ordered probit regression model that enabled the age and gender of the patient and the time since onset of disease to be controlled.

Investigation of differences between primary studies
Not reported.

Results of the review
Most of the estimates obtained from the literature were not reported in detail, but presented as graphics and diagrams. Infliximab reduced symptom progression significantly and slowed disease progression in comparison with standard care.

The numbers of patients in the 6 different HAQ states at baseline and after 1 year in the ATTRACT trial with infliximab plus methotrexate or methotrexate alone were reported.

For example, with infliximab plus methotrexate, 16 patients were in the lowest level of disability at time 0, while there were 82 patients at 1 year. With methotrexate alone, the corresponding values were 2 patients at time 0 and 11 at 1 year.
Similarly, with infliximab plus methotrexate, 11 patients were in the highest level of disability at time 0, while there were only 5 patients at 1 year. With methotrexate alone the corresponding values were 2 patients at time 0 and 3 at 1 year.

These data were used to develop the transition probabilities between health states in the first year.

In the cohort studies, the average HAQ score worsened from 0.93 to 1.10 in the Lund cohort (in 10 years) and from 0.7 to 0.9 in the ERAS cohort (in 9 years).

These values were used to develop the transition probabilities in the following years.

Other data were not reported.

**Measure of benefits used in the economic analysis**
The summary benefit measure used in the economic analysis was the expected number of quality-adjusted life-years (QALYs). These were obtained by combining utility and survival data in the decision model. As already stated, the utility weights were taken from two cohorts of patients using the EuroQol. Discounting was applied (3% in Sweden and 1.5% in the UK).

**Direct costs**
The analysis of the costs was carried out from a societal perspective. The direct medical costs included were for hospitalisation, surgical interventions, ambulatory and community care, and RA medication (infliximab and DMARDs). NSAID consumption was not included since most patients used this class of drug and usage did not differ significantly between the states. Other than the cost of infliximab, the unit costs were not presented separately from the resource quantities. Resource consumption was mainly derived from the two cohort studies (Lund and ERAS). The unit costs were obtained from hospital accounting data and official price lists, although the sources for each item were not reported. The analysis took the impact of compliance with infliximab seen in the clinical trial (88.5% completed the treatment at 1 year) into consideration. Discounting was relevant as the long-term costs were estimated. The annual rate applied was 3% in Sweden and 6% in the UK. The price year was not explicitly reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were included, which was appropriate given the societal perspective used for the analysis. Productivity losses were calculated only for patients with an HAQ score above 0.6. For patients below this score, only short-term sick leave was included. The indirect costs were estimated using the human capital approach, thus the costs were estimated from the average gross annual income including employers' contributions. The quantities of resources used were obtained from the respective cohorts. As in the analysis of the direct costs, the unit costs and quantities of resources used were not presented separately and the price year was not reported. Discounting was also the same as for the direct costs.

**Currency**
UK pounds sterling () and Swedish kroner (SEK). The costs were then converted into Euros (EUR). The exchange rate was EUR 1 = 0.62 = SEK 9.3.

**Sensitivity analysis**
In a sensitivity analysis, the cost of infliximab was varied using the Swedish, UK and Swiss prices, which represented the lower, middle and higher price ranges. In addition, an alternative model was presented by incorporating a loss of
effect in the year after discontinuation, expressed as faster disease progression than that in the epidemiological cohorts. The authors calculated the difference in the HAQ changes between the infliximab and methotrexate groups during the clinical trial, and applied the difference (odds ratios for progression) to the Lund and ERAS cohorts for the treatment arm for the first year. Treatment was thus compared directly with that of the epidemiological cohorts, also eliminating the placebo effect in the clinical trial.

Estimated benefits used in the economic analysis
In Sweden, the expected QALYs were 4.632 with infliximab plus methotrexate and 4.384 with methotrexate alone (difference 0.248 QALYs) with the 1-year treatment. With the 2-year treatment, the values were 4.683 with infliximab plus methotrexate and 4.384 with methotrexate alone (difference 0.299 QALYs).

In the UK, the expected QALYs were 4.029 with infliximab plus methotrexate and 3.731 with methotrexate alone (difference 0.298 QALYs) with the 1-year treatment. With the 2-year treatment, the values were 4.131 with infliximab plus methotrexate and 3.731 with methotrexate alone (difference 0.400 QALYs).

Cost results
The total costs of the 1-year treatment in Sweden were SEK 1,129,507 (direct costs SEK 257,826) with infliximab plus methotrexate and SEK 1,121,476 (direct costs SEK 191,857) with methotrexate alone. The difference in the total costs was SEK 8,031 (difference in direct costs SEK 65,969). With the 2-year treatment, the total costs were SEK 1,166,298 (direct costs SEK 315,769) with infliximab plus methotrexate and SEK 1,121,476 (direct costs SEK 191,857) with methotrexate alone. The difference in the total costs was SEK 44,822 (difference in direct costs SEK 123,912).

The total costs of the 1-year treatment in the UK were 43,299 (direct costs 20,327) with infliximab plus methotrexate and 36,859 (direct costs 12,666) with methotrexate alone. The difference in the total costs was 6,440 (difference in direct costs 7,661). With the 2-year treatment, the total costs were 48,799 (direct costs 26,590) with infliximab plus methotrexate and 36,859 (direct costs 12,666) with methotrexate alone. The difference in the total costs was 11,940 (difference in direct costs 13,924).

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative treatments.

In Sweden, the incremental cost per QALY gained with infliximab plus methotrexate for 1 year over methotrexate alone was SEK 32,000 (EUR 3,440) with total costs and SEK 266,000 (EUR 28,600) with direct costs alone. The corresponding values for 2 years' treatment were SEK 150,000 (EUR 16,100) with total costs and SEK 414,000 (EUR 44,500) with direct costs alone.

In the UK, the incremental cost per QALY gained with infliximab plus methotrexate for 1 year over methotrexate alone was 21,600 (EUR 34,800) with total costs and 25,700 (EUR 41,500) with direct costs alone. The corresponding values for 2 years' treatment were 29,900 (EUR 48,200) with total costs and 34,800 (EUR 56,100) with direct costs alone.

In the alternative model incorporating an effect loss at discontinuation, the incremental cost per QALY improved in both countries and infliximab was cost-saving in Sweden when a societal perspective was used.

When the cost of infliximab was varied, the incremental cost-utility ratio increased as expected with higher drug costs. When the total costs were considered, the incremental cost per QALY gained with infliximab plus methotrexate for 1 year over methotrexate alone ranged from EUR 3,440 to EUR 16,100 in Sweden, and from EUR 23,900 to EUR 37,900 in the UK.

Authors' conclusions
The addition of infliximab to methotrexate for the treatment of patients with rheumatoid arthritis (RA) was cost-effective in both the UK and Sweden, although the cost per quality-adjusted life-year (QALY) of infliximab plus...
methotrexate in comparison with methotrexate alone was more efficient in Sweden.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. Methotrexate alone is likely to reflect a standard comparator in the two countries considered in the analysis. The choice of the comparator was also influenced by the availability of data from a clinical trial for infliximab plus methotrexate versus methotrexate alone. This was the only clinical trial that compared infliximab with another DMARD. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of studies, which were presumably identified selectively. No details of the methods and conduct of a systematic review of the literature were provided. The authors gave information on the characteristics of the primary studies. The choice of these primary studies as sources of clinical data was appropriate given the robustness of the sources: the treatment effect was derived from a large clinical trial, while the other epidemiological model inputs came from cohort studies relevant to the two countries. The key source of uncertainty (i.e. treatment effect after discontinuation) was explicitly considered in an alternative analysis. The issue of homogeneity amongst the primary studies was not addressed by statistical methods, but the authors stated that the epidemiological cohorts had the same baseline characteristics as patients included in the primary clinical trial. Nevertheless, it would appear that, at baseline, patients in the two cohorts were substantially less severely disabled in terms of the HAQ score than patients in the ATTRACT study.

Validity of estimate of measure of benefit
The benefit measure used in the analysis was appropriate since QALYs capture the impact of the interventions on the most relevant dimensions of health (i.e. survival and quality of life). Further, it is possible to compare QALYs with the benefits of other health care interventions. There were few details on the approach used to calculate the QALYs, but the EuroQol represents a typical instrument to elicit patients' preferences. Moreover, the use of utility weights directly derived from the patients included in the two epidemiological cohorts was a strength of the study.

Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study. The inclusion of indirect costs was a key issue of the analysis since productivity losses are the main cost driver. Only work losses related to RA were considered. Indirect costs due to premature mortality were not taken into account since the impact of RA on premature mortality has been the subject of debate in the economic literature. The economic data were derived from published sources and, whilst these were not described, they are likely to represent typical sources for direct and indirect costs in both countries. Resource use was mainly taken from the two epidemiological cohorts. However, in general, few details of the cost analysis were provided. For example, the unit costs were not presented separately from the resource quantities, which will limit the possibility of replicating the analysis in other settings. The authors did not investigate the issue of variability in the cost estimates, except for the cost of infliximab. Statistical analyses of the costs were not performed. The authors did not report the price year, which will hinder reflation exercises in other settings. The authors stated that differences in the discount rate for the costs might have explained the differences in total costs between the two countries.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Limited sensitivity analyses were carried out, which limits the external validity of the study. However, the alternative model, with loss at discontinuation for infliximab, was an interesting point of the analysis and is a way of assuming a different efficacy for the study drug. The study referred to the general population of patients with RA and this was reflected in the authors' conclusions. However, the study sample reflected the group of patients enrolled in the ATTRACT study.
Implications of the study
The study results suggest that infliximab could be a cost-effective treatment for patients with RA, both in Sweden and in the UK.

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Other publications of related interest


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