Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden
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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 adalimumab (40mg/week), a fully human monoclonal antibody with high affinity and specificity for tumour necrosis factor (TNF), for the treatment of moderate to severe rheumatoid arthritis (RA).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with moderate to severe RA for whom at least two traditional DMARDs had failed.

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

Dates to which data relate
The clinical data came from studies published between 1995 and 2004. No dates for much of the resource use data (which were mainly based on clinical experts’ opinion) and costs were reported. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a synthesis of completed studies.

Modelling
A mathematical approach was constructed to implement a patient-based, transition state model in 10,000 hypothetical patients with RA. The time horizon was lifetime and the cycle length was 6 months. Patients entered the model after first-line DMARD treatments had failed, and it was assumed that only one biological agent would be used for each patient. Patients for whom treatment showed little efficacy or efficacy diminished over time could move on to three more DMARDs, at which point it was assumed that the patient had attempted all effective treatments and that a palliative strategy would have been introduced. A simplified structure of the decision model was depicted.

Outcomes assessed in the review
The outcomes assessed from the literature were:
the response rates,
the rate of withdrawal,
the rates of adverse events, and
a series of global parameters.

The global parameters included:

- the initial value of the Health Assessment Questionnaire (HAQ),
- utility/HAQ regression gradient,
- HAQ progression due to no response,
- HAQ progression: response to DMARD,
- HAQ progression: response to biological agent,
- response decrease, and
- the relative risk of mortality due to RA.

The response rates were assessed using American College of Rheumatology (ACR) criteria (ACR20, ACR50, and ACR70).

**Study designs and other criteria for inclusion in the review**
The effectiveness data were derived from a review of the literature and were based on clinical trials. Adverse events and patients' withdrawal were derived from an observational study. Natural mortality was estimated from standard life tables of the Swedish population. The calculations made to convert ACR results to HAQ and HAQ to health utilities were reported.

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

**Criteria used to ensure the validity of primary studies**
The validity of the primary studies was ensured by selecting clinical trials as the main source of treatment efficacy.

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

**Number of primary studies included**
Fourteen primary studies provided the data used in the decision model.

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

**Investigation of differences between primary studies**
Since indirect comparisons were performed, recommended methods of accounting for differences in patient groups between trials were followed. In particular, these differences were adjusted for placebo rates when similar placebo strategies were used in different studies.

**Results of the review**

The proportions of patients responding in combination dose-finding trials (ACR20, ACR50 and ACR70 thresholds) were:

- with etanercept, ACR20 66%, ACR50 42% and ACR70 19%;
- with adalimumab, ACR20 67%, ACR50 55% and ACR70 27%;
- with infliximab, ACR20 47%, ACR50 29% and ACR70 12%; and
- with DMARDs, ACR20, 37%, ACR50 13% and ACR70 0%.

The proportions of patients responding in combination dose-findings and radiographic trials with adalimumab were 57% for ACR20, 42% for ACR50 and 24% for ACR70.

The response rates in monotherapy trials (ACR20, ACR50 and ACR70 thresholds) were:

- with etanercept, 59% for ACR20, 40% for ACR50 and 15% for ACR70; and
- with adalimumab, 41% for ACR20, 19% for ACR50 and 12% for ACR70.

The withdrawal rate during 6 months was 0.08 with etanercept, 0.08 with adalimumab, 0.12 with infliximab and 0.27 with DMARDs.

The rate of mild adverse events during a 6-month periods was 0.29 with etanercept, 0.29 with adalimumab, 0.54 with infliximab and 0.34 with DMARDs.

The rate of moderate adverse events during a 6-month period was 0.16 with etanercept, 0.16 with adalimumab, 0.31 with infliximab and 0.34 with DMARDs.

The rate of severe adverse events during a 6-month period was 0.07 with etanercept, 0.07 with adalimumab, 0.1 with infliximab and 0.06 with DMARDs.

The initial value of the HAQ was 1.55 (standard deviation, SD=0.61).

The utility/HAQ regression gradient was 0.76 - 0.28 HAQ.

The HAQ progression due to no response was 0.066 (range: 0.016 - 0.066).

The HAQ progression: response to DMARD was 0.017 (SD=0.02).

The HAQ progression: response to biological agent was 0.017 (range: 0 - 0.017).

The odds ratio for response decrease was 0.98 (SD=0.0045).

The relative risk of mortality due to RA was 1.63 (SD=0.14).

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated by combining utility values and expected survival, which were derived from the literature. An annual discount rate of 3% was applied. The authors pointed out that the results for adalimumab plus MTX were analysed twice. First, a comparison was made
using similar studies of the TNF antagonists (DE009). Second, additional information from the larger adalimumab trial was used in a pooled analysis (DE009 and DE019).

**Direct costs**
The perspective adopted in the study was that of the third-party payer. The health services included in the economic evaluation were drugs, monitoring and drug administration, toxicity and hospitalisations. The unit costs were reported only for drugs, but extensive information on some categories of resources was provided. Resource use relating to drugs, monitoring and administration, and toxicity were estimated on the basis of experts' opinions. The consumption of hospital services was estimated using approximations based on patient HAQ-DI (Disability Index) scores. In particular, if a patient's HAQ-DI was estimated to have improved, the patient's corresponding health care costs were assumed to have decreased. Some costs were estimated from Swedish studies, but in general the source of the cost data was unclear. The total costs were calculated using a modelling approach. Discounting was relevant since lifetime costs were considered, and an annual discount rate of 3% was applied.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case, but probabilistic distributions were assigned to all economic inputs in the probabilistic sensitivity analysis.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
Euros (Euro).

**Sensitivity analysis**
A probabilistic sensitivity analysis was carried out to deal with the uncertainty around cost-effectiveness ratios. The model was run 1,000 times and probabilistic distributions were assigned to all model inputs. Further, a univariate sensitivity analysis was performed to determine the impact on the final cost-effectiveness estimates of individual parameters. Such parameters included rates of adverse events, direct costs, withdrawal rates, HAQ values, discounting (both costs and benefits), DMARD response rates, baseline age, mortality, and productivity losses. The alternative ranges of values were either derived from the literature or set by the authors.

**Estimated benefits used in the economic analysis**
Two analyses were performed. In the ACR50/DAS28 good analysis it was assumed that only ACR50 responders at 6 months would continue their treatment. In the ACR20/DAS28 moderate analysis it was assumed that responders to ACR20 would continue their treatment.

Using the ACR50/DAS28 good analysis, the estimated QALYs were:

- 2.3114 with adalimumab plus MTX (DE009),
- 2.0493 with etanercept monotherapy,
- 2.0493 with etanercept monotherapy, and
1.1818 with traditional DMARDs.

Using the ACR20/DAS28 moderate analysis, the estimated QALYs were:

2.9083 with adalimumab plus MTX (DE009),
2.7424 with adalimumab plus MTX (DE009 and DE019),
2.9515 with infliximab plus MTX,
2.4121 with etanercept plus MTX,
2.4321 with adalimumab monotherapy,
2.7303 with etanercept monotherapy, and
1.7041 with traditional DMARDs.

**Cost results**

Using the ACR50/DAS28 good analysis, the estimated costs were:

Euro 108,982 with adalimumab plus MTX (DE009),
Euro 102,610 with adalimumab plus MTX (DE009 and DE019),
Euro 103,129 with etanercept plus MTX,
Euro 102,099 with infliximab plus MTX,
Euro 90,058 with adalimumab monotherapy,
Euro 102,421 with etanercept monotherapy, and
Euro 70,387 with traditional DMARDs.

Using the ACR20/DAS28 moderate analysis, the estimated costs were:

Euro 117,979 with adalimumab plus MTX (DE009),
Euro 114,462 with adalimumab plus MTX (DE009 and DE019),
Euro 133,590 with etanercept plus MTX,
Euro 114,732 with infliximab plus MTX,
Euro 116,442 with adalimumab monotherapy,
Euro 112,351 with etanercept monotherapy, and
Euro 68,757 with traditional DMARDs.

**Synthesis of costs and benefits**

Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative treatment strategies in comparison with traditional DMARDs.
Using the ACR50/DAS28 good analysis, the estimates of the incremental cost per QALY versus traditional DMARDs were:

- Euro 34,167 with adalimumab plus MTX (DE009),
- Euro 34,922 with adalimumab plus MTX (DE009 and DE019),
- Euro 35,760 with etanercept plus MTX,
- Euro 48,333 with infliximab plus MTX,
- Euro 41,561 with adalimumab monotherapy, and
- Euro 36,927 with etanercept monotherapy.

Using the ACR20/DAS28 moderate analysis, the estimates of the incremental cost per QALY versus traditional DMARDs were:

- Euro 40,875 with adalimumab plus MTX (DE009),
- Euro 44,018 with adalimumab plus MTX (DE009 and DE019),
- Euro 51,976 with etanercept plus MTX,
- Euro 64,935 with infliximab plus MTX,
- Euro 65,499 with adalimumab monotherapy, and
- Euro 42,480 with etanercept monotherapy.

The sensitivity analysis showed that the estimated cost-effectiveness ratios were affected by baseline age, the standardised mortality ratio, and HAQ-DI/utilities. The inclusion of avoided productivity losses favoured all biological treatments. The probabilistic analysis indicated that at a willingness to pay of Euro 44,000 (30,000) per QALY, adalimumab was cost-effective in about 83% of random samples, while etanercept monotherapy was cost-effective in 72% of samples.

**Authors’ conclusions**

Adalimumab was a cost-effective treatment for patients with moderate to severe RA in Sweden. The cost-effectiveness of adalimumab compared favourably with that of traditional disease-modifying antirheumatic drugs (DMARDs) and was similar to that of other biological treatments.

**CRD COMMENTARY - Selection of comparators**

The authors explained the choice of the comparators, which appear to have been appropriate for the study question. The dosages were reported. The model accounted for switches to second- and third-line therapies for patients not responding adequately. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The evidence used in the decision model to determine treatment efficacy was derived from a review of the literature. No information on the methods and conduct of the review was reported. Since only clinical trials were included for treatment effect, a high internal validity is ensured. The authors noted that most comparisons between drugs were indirect because limited evidence came from head-to-head clinical trials. However, recommended methods were used to make the comparisons as valid as possible when patients included in the control arms of the trials (i.e. placebo) were comparable. Further, the authors noted that different measures of treatment effectiveness had been used in the trials.
and assumptions were made so that a final common measure could be used in the current study. Moreover, some data came from selected groups of patients, which might not have been representative of a typical RA patient. Other model inputs were estimated from specific studies, the design and characteristics of which were not described in detail. The issue of uncertainty was satisfactorily addressed in the sensitivity analysis.

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 care (i.e. survival and quality of life). Further, QALYs are comparable with the benefits of other health care interventions. Discounting was applied as guidelines for economic evaluations suggest. Extensive information on the source of the utility weights and the approach used to calculate QALYs was provided.

Validity of estimate of costs
The perspective adopted in the study was that of the policy decision-makers. Only direct medical costs were included in the analysis. Details on resource consumption, in terms of drug doses and monitoring, were reported for most items but the information on other resources was limited. Further, the unit costs were not reported and this limits the possibility of replicating the cost analysis in other settings. Similarly, the sources of the data were not given for all items. Statistical analyses of the costs were not performed in the base-case, but probabilistic distributions were assigned to economic model inputs in the stochastic sensitivity analysis. The price year was reported, thus aiding reflation exercises in other time periods. The impact of indirect costs was investigated in the sensitivity analysis. The analysis showed that the inclusion of avoided productivity losses improved the cost-effectiveness of all biological treatments.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. It was noted that the study was specific to the Swedish setting, thus caution is required when extrapolating the results of the current study to other settings. However, some sensitivity analyses were performed, thus enhancing the external validity of the study. The analysis referred to patients with moderate to severe RA and this was reflected in the authors' conclusions.

Implications of the study
Since all biological agents were almost equally cost-effective, the study results suggested that there is a strong argument for the reimbursement of adalimumab in countries where etanercept or infliximab are already reimbursed.

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Other publications of related interest

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