Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early 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.

CRD summary
This study determined the cost-effectiveness of tumour necrosis factor (TNF) antagonists as initial therapy for patients with early rheumatoid arthritis. The authors concluded that compared with disease-modifying antirheumatic drugs alone, the adalimumab plus methotrexate initiated sequence was the most cost-effective of the TNF antagonist sequences. The methods and the reporting were satisfactory, but the authors’ conclusions did not fully answer the study question.

Type of economic evaluation
Cost-utility analysis

Study objective
This study determined the cost-effectiveness of tumour necrosis factor (TNF) antagonists as initial therapy for patients with early rheumatoid arthritis.

Interventions
The TNF antagonists were adalimumab, etanercept, and infliximab and these were recently introduced biologic treatments for rheumatoid arthritis. Methotrexate was the most widely used disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis, at the time.

Five treatment sequences with TNF antagonists and methotrexate were compared. The reference sequence was methotrexate-based and did not include biologic therapy. Three sequences included a single biologic treatment (two with methotrexate) followed by methotrexate and the remaining sequence included two biologic treatments; adalimumab plus methotrexate was followed by etanercept.

Location/setting
USA/secondary care.

Methods
Analytical approach:
An individual-patient model was constructed based on a structure described by Bansback, et al. (2005, see 'Other Publications of Related Interest' below for bibliographic details). This compared alternative sequences of therapies over a lifetime and the authors stated that the perspective was that of the third-party payer.

Effectiveness data:
The clinical data were from three randomised controlled trials (RCTs): the PREMIER, Active controlled Study of Patients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset (ASPIRE), and Early Rheumatoid Arthritis (ERA) trials. These were the only three published RCTs that assessed TNF antagonists in early rheumatoid arthritis. Patients in all three trials were comparable in their baseline variables. The main clinical outcome was the Health Assessment Questionnaire (HAQ) score. The deterioration in individual patients’ HAQ scores was modelled over time and sampled at six-month intervals. Regression equations were used to calculate the quality of life, using the HAQ score as the independent variable.
Monetary benefit and utility valuations:
The utilities were based on the Health Utilities Index (HUI-3). These estimates were derived from the HAQ scores using a published regression equation. The utility estimates at baseline were from the PREMIER trial, which used the HAQ Disability Index.

Measure of benefit:
The benefit measure was the number of quality-adjusted life-years (QALYs) and these were discounted at an annual rate of 3%.

Cost data:
The cost categories included drugs, drug monitoring and administration, and adverse events. Drug costs at six-month intervals were calculated using Analy$ource. Drug monitoring and administration costs and adverse event costs were assigned, based on physician fee schedules and diagnosis-related group data. Monitoring and administration costs were based on clinicians’ assessments of health care contacts and diagnostic tests associated with treatment. The rates of adverse events were based on a study of the long-term treatment of rheumatoid arthritis, by Geborek, et al. (2002, see 'Other Publications of Related Interest' below for bibliographic details). The price year was 2007 and all prices were adjusted to US dollars ($). An annual discount rate of 3% was applied.

Analysis of uncertainty:
A univariate sensitivity analysis was performed by varying the model inputs across wide ranges. Probabilistic sensitivity analysis was performed and the results were shown in cost-effectiveness acceptability curves.

Results
The adalimumab plus methotrexate followed by etanercept sequence resulted in the greatest number of QALYs, at 4.22. This was compared with 3.24 QALYs in the adalimumab plus methotrexate sequence, 3.00 QALYs in the etanercept sequence, 2.90 QALYs in the infliximab plus methotrexate sequence, and 2.00 QALYs in the methotrexate sequence.

The adalimumab plus methotrexate then etanercept sequence also cost the most, at $362,967. This was compared with $348,298 in the adalimumab plus methotrexate sequence, $347,072 in the etanercept sequence, and $319,348 in the methotrexate sequence.

All treatment regimens were extendedly dominated, which means that their incremental cost-effectiveness was greater than the next more effective sequence, except for the methotrexate alone and adalimumab plus methotrexate then etanercept sequences. Compared with methotrexate alone the incremental cost-effectiveness ratio (ICER) of the adalimumab plus methotrexate then etanercept sequence was $19,663.

One-way sensitivity analysis showed that using European Quality of life (EQ-5D) questionnaire utilities rather than HUI-3 utilities increased the ICER of the adalimumab plus methotrexate sequence. This ICER was also sensitive to changes in the HAQ measurement of disease progression.

Authors' conclusions
The authors concluded that the adalimumab plus methotrexate initiated sequence was the most cost-effective, whether followed by methotrexate or by another TNF antagonist (etanercept), but it was not possible to evaluate etanercept plus methotrexate as an initial treatment.

CRD commentary
Interventions:
The interventions were well described and were appropriately compared with the current practice of methotrexate as initial treatment in the authors’ setting. Other sequences might have been significant comparators, such as etanercept plus methotrexate or infliximab plus methotrexate followed by etanercept.

Effectiveness/benefits:
No systematic review of the literature was reported, but the authors stated that the RCTs they used were the only relevant ones that existed. RCTs are potentially good sources of evidence, but no details of the trials were reported.
effectiveness of etanercept following adalimumab plus methotrexate was assumed to be the same as for first-line etanercept treatment and this assumption was not explored in the sensitivity analyses. The approach used to determine the utility data was reported and the methodology used to calculate the QALYs was clear. QALYs were the most appropriate benefit measure, given the impact of the disease on the quality of life.

Costs:
The perspective was stated and it appears that all the relevant costs for this perspective and study question were considered. A detailed breakdown of the cost items was given, which should allow the cost analysis to be replicated for other settings. The sources of the cost data were referenced and the estimates seem to have been relevant to the setting and population. The cost analysis was well reported.

Analysis and results:
An incremental cost-effectiveness analysis was conducted, but one of the adalimumab treatment regimens was not properly included. An incremental analysis was appropriate for determining the cost-effectiveness of the interventions. The uncertainty was appropriately assessed in both univariate and probabilistic sensitivity analyses, except that the uncertainty around the effectiveness of etanercept as a second-line treatment was not investigated. Overall, the results of both the base case and the sensitivity analyses were clearly presented. The authors highlighted the limitations of their analysis.

Concluding remarks:
The methods and the reporting of the study were satisfactory and the authors' conclusions were consistent with the evidence, but they did not state the cost-effectiveness of a TNF antagonist compared with a DMARD alone.

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