Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with 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 assessed the cost-effectiveness of strategies involving non-biologic disease-modifying antirheumatic drugs (DMARDs) for the treatment of patients with early rheumatoid arthritis. The authors concluded that combination DMARD therapy was likely to be cost-effective, compared with monotherapy, if there was rapid dose reduction or intensive therapy, with rapid dose increases. The methods were robust and sophisticated, which ensures the validity of the authors’ conclusions.

Type of economic evaluation
Cost-utility analysis

Study objective
This study assessed the cost-effectiveness of strategies involving non-biologic disease-modifying antirheumatic drugs (DMARDs), for the treatment of patients with early rheumatoid arthritis.

Interventions
The strategies were monotherapy, parallel therapy, step-up therapy, step-down therapy, intensive step-up therapy, and monotherapy plus steroid. Patients were given biologics after the failure of two DMARDs.

The monotherapy DMARDs included methotrexate, sulfasalazine hydroxychloroquine, and cyclosporine. In parallel therapy, two or more DMARDs were given at the same time. In step-up therapy, patients began with DMARD monotherapy, and a second DMARD was added if an inadequate response was observed within the first six months. The step-down therapy started with parallel therapy, followed by a reduction in dose and withdrawal. In intensive step-up therapy, patients began with parallel therapy and the doses were rapidly increased if an inadequate response was observed within the first six months. In monotherapy plus steroid, glucocorticosteroids were routinely used alongside DMARD monotherapy; the other strategies used steroids as needed.

Location/setting
UK/primary and secondary care.

Methods
Analytical approach:
The analysis was based on a decision model that tracked the course of disease for hypothetical, individual patients, using their scores on the Health Assessment Questionnaire (HAQ). A lifetime horizon was considered. The analysis was performed as part of a UK National Institute for Health and Clinical Excellence (NICE) Clinical Guideline for Rheumatoid Arthritis. The authors stated that it was carried out from the perspective of the NHS.

Effectiveness data:
A systematic review was carried out to identify published sources for the clinical inputs. Only randomised controlled trials (RCTs) were included, if they were published in English and reported American College of Rheumatology (ACR) outcomes. Direct and indirect comparisons were carried out, using a mixed-treatment method (also known as a network meta-analysis). The treatment response rates were the key input to the model and were defined as the patients achieving ACR20 (20% improvement in certain criteria) or ACR50 after six months of treatment. Long-term data were
Monetary benefit and utility valuations:
The utility values were from a study of abatacept for rheumatoid arthritis that provided European Quality of life (EQ-5D) scores for each quarter-point on the HAQ scale. The long-term impact of biologic treatment on patients’ quality of life was from a study analysing data from the BSRBR.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and they were discounted at an annual rate of 3.5%.

Cost data:
The economic analysis included the costs of drug acquisition and administration, consultations with health care professionals, hospitalisations, out-patient visits, and joint replacement surgery. The resource quantities were based on published evidence. The drug costs were from the British National Formulary. Consultations and drug administration costs were from the Personal Social Services Research Unit. Other costs were based on HAQ scores and a study that used resource data from the Norfolk Arthritis Register (NOAR). The long-term costs of biologic treatments (after DMARDs) were from the study analysing data from the BSRBR. All costs were in UK pounds sterling (£) and a 3.5% annual discount rate was applied.

Analysis of uncertainty:
A probabilistic sensitivity analysis was carried out to investigate the overall uncertainty in the model inputs, using Monte Carlo simulation and conventional probability distributions for each group of parameters. Univariate sensitivity analyses were conducted on the key model parameters.

Results
The projected costs were £55,996 with monotherapy, £50,791 with step-up therapy, £55,573 with parallel therapy, £61,046 with intensive therapy, £48,849 with step-down therapy, and £57,468 with steroid therapy. The QALYs were 13.73 with monotherapy, 11.91 with step-up therapy, 13.42 with parallel therapy, 15.77 with intensive therapy, 15.32 with step-down therapy, and 11.79 with steroid therapy.

Compared with monotherapy, step-down therapy was dominant, as it was more effective and less expensive, steroid therapy was dominated, and the incremental cost per QALY gained was £2,482 with intensive therapy. Monotherapy had an incremental cost per QALY of £2,852 compared with step-up therapy and £1,356 compared with parallel therapy.

Compared with each other, step-down therapy was the reference strategy and the incremental cost per QALY gained with intensive therapy was £27,392. All other strategies were dominated.

The sensitivity analysis showed that there was great uncertainty due to the overlapping of the cost-effectiveness results for step-down and intensive strategies. At a threshold of £20,000 per QALY gained, the probability of being cost-effective was 0.50 for step-down therapy and 0.43 for intensive therapy. The step-down and intensive strategies were the preferred options even when changing parameter values and scenarios.

Authors' conclusions
The authors concluded that combination DMARD therapy was likely to be cost-effective, compared with monotherapy, if it included rapid dose reduction and withdrawal or intensive therapy, with rapid dose increases for inadequate responders.

CRD commentary
Interventions:
The selection of the comparators was appropriate as the strategies were identified by a review of the literature. The strategies were briefly described. The authors acknowledged that similar, but not identical treatment strategies were grouped. The DMARD monotherapies were grouped together, because no trial had shown different efficacy results,
but some experts consider methotrexate to be superior to the other options.

**Effectiveness/benefits:**
A valid approach was used to identify the relevant sources of data; the published literature was searched. The search focused on RCTs and their methodological rigour should have ensured the validity of the clinical inputs. A network meta-analysis was used to pool the evidence from multiple sources and this was a valid method. Statistical analyses were used to capture the differences between these studies. The long-term efficacy of the biologics was from a well-known published model. QALYs were an appropriate summary benefit measure, given the impact of the rheumatoid arthritis on health-related quality of life. The utility weights were from a large sample of patients and a valid instrument was used. Standard equations were used to convert HAQ scores to utility values. The authors pointed out that no mortality effect was considered as there was no evidence of a difference in mortality between treatments.

**Costs:**
The economic analysis was consistent with the perspective in terms of the cost categories and their sources. The drug costs were presented as six-month totals for each strategy and the other costs were presented by HAQ score. The long-term costs were reported as category totals, without the unit costs and resource quantities; key items were fully presented. The unit costs were from typical UK sources. The authors acknowledged that the NOAR database might not reflect up-to-date treatment patterns and might become less relevant in the future. The discount rate was in line with UK guidelines, but the price year was not explicitly reported.

**Analysis and results:**
The expected costs and benefits were clearly reported for all strategies and were synthesised using an incremental approach. Valid approaches were used to investigate the uncertainty and the findings were clearly presented and discussed. The potential limitations of the analysis were acknowledged by the authors and have been reported. The results might be transferable to settings with similar cost structures.

**Concluding remarks:**
The methods were robust and sophisticated, which ensures the validity of the authors’ conclusions.

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