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
The study evaluated the cost-utility of tocilizumab in rheumatoid arthritis patients with inadequate responses to traditional disease-modifying anti-rheumatic drugs (DMARDs). The authors concluded that replacing a biologic DMARD with tocilizumab or adding tocilizumab to the standard care pathway was cost-effective. The quality of the study methodology was adequate, with methods and results reported appropriately. Given the scope of the study, the authors' conclusions appear to be valid.

Type of economic evaluation
Cost-utility analysis

Study objective
The study evaluated the cost-utility of tocilizumab in rheumatoid arthritis patients with inadequate responses to traditional disease-modifying anti-rheumatic drugs (DMARDs) in Italy.

Interventions
Standard care/practice (etanercept as the first biologic DMARD in the standard care sequence followed by adalimumab, rituximab, and abatacept) was compared with tocilizumab treatment (etanercept replacing tocilizumab with all subsequent treatments remaining the same).

Three further treatment pathways were assessed: adalimumab was used before etanercept in the standard care pathway compared with tocilizumab (replacement for adalimumab) in the treatment pathway; infliximab was used instead of adalimumab before etanercept in the standard care pathway; and tocilizumab added to methotrexate at the start of the standard care pathway.

Location/setting
Italy/outpatient care.

Methods
Analytical approach:
An individual patient simulation model was developed to assess the costs and benefits associated with the interventions under study. The time horizon was the lifetime of the patient. The authors stated that the Italian National Health Service perspective was used.

Effectiveness data:
Clinical and effectiveness data came from previously published studies. The main measure of effectiveness was the American College of Rheumatology (ACR) response rate using four categories: no response, ACR20 response (20% improvement), ACR50 response, or ACR70 response. The effectiveness estimates came from three previously published large multinational phase-3 randomised clinical trials; two published mixed-treatment comparisons were used to derive response probabilities because of lack of head-to-head ACR data from the same trials. Disease-specific quality of life (assessed using the Health Assessment Questionnaire - HAQ) was also obtained from these trials. The extrapolation of trial data at six months to lifetime were based on authors' assumptions.

Monetary benefit and utility valuations:
A mapping exercise was used to convert patient HAQ scores into utilities.

Measure of benefit:
Quality-adjusted life-years (QALYs) were used and discounted using an annual rate of 3%.

Cost data:
The direct costs included pharmaceuticals, drug administration (including nurse time), examinations, physiotherapy, hospitalisation, transportation, house help, and auxiliary devices. Drug costs were obtained from hospital prices. Drug administration costs came from a published study. All other medical costs were from an Italian retrospective prevalence-based multicentre study of 200 patients (see Other Publications of Related Interest). All costs were updated to 2009 prices using data from the Italian Institute for Statistics. Future costs were discounted using an annual rate of 3% and were reported in euros (EUR).

Analysis of uncertainty:
One-way sensitivity analyses were undertaken to test the impact of model assumptions on the results. A probabilistic analysis was performed by fitting probability distributions to model variables. The results were presented in a cost-effectiveness acceptability curve.

Results
For standard care, the average cost per patient was EUR 143,547 and the average QALYs gained were 9.3502.

For tocilizumab, the average cost per patient was EUR 141,181 and the average QALYs gained were 9.881.

Costs and benefits were combined using an incremental cost-utility ratio (the additional cost per QALY gained). Tocilizumab was found to be dominant over standard care (it was both more effective and less costly). Results of the probabilistic sensitivity analysis showed that at a willingness to pay threshold of EUR 50,000 per QALY gained, the probability that tocilizumab was cost-effective was 100%.

For the additional three scenarios assessed: tocilizumab was dominant when adalimumab was used ahead of etanercept as standard therapy; the incremental cost-utility ratio of tocilizumab was EUR 2,655 when infliximab was used ahead of etanercept as standard therapy; and the incremental cost-utility ratio of tocilizumab was EUR 17,119 when tocilizumab was added to standard therapy.

Authors’ conclusions
The authors concluded that replacing another biologic DMARD with tocilizumab or adding tocilizumab to the standard care pathway was cost-effective.

CRD commentary
Interventions:
The interventions under study were reported adequately. The selection of comparators was appropriate as they were among the most commonly used treatments used in the authors’ setting (Italy).

Effectiveness/benefits:
Clinical and effectiveness data came from previously published studies. The authors did not report how published studies were identified and whether a systematic review of the literature was undertaken. As a result, it was not clear if all the relevant clinical and effectiveness data were considered for inclusion into the model. However, the main measures of effectiveness were obtained from three large published phase-3 clinical trials, so it was likely that the main clinical inputs used in the model were internally valid. The mixed-treatment comparisons used for pooling drug efficacy data was a strength of the analysis, but limited details were given.

Costs:
The perspective adopted was explicitly reported to be that of the Italian healthcare system; all relevant cost categories for this perspective appeared to be included. However, the authors acknowledged the limitation that the costs of treating adverse events due to treatment were not included. The sources from which costs were obtained from were reported adequately and in detail. The price year, time horizon, discount rate used, inflationary exercises and currency
details were all reported.

Analysis and results:
An individual patient simulation model was used to synthesise cost and outcome information. Adequate details of the model structure were provided, along with a diagram of treatment sequences. Uncertainty was adequately tested using one-way and probabilistic sensitivity analyses. As a limitation to their study, the authors reported that assumptions were made to extrapolate results over a longer time period because of the short time duration of the included trials (six months).

Concluding remarks:
The quality of the study methodology was adequate, with methods and results reported appropriately. Given the scope of the study, the authors' conclusions appear to be valid.

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