Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling approach
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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 examined the cost-effectiveness of sequences of biological treatments for patients with moderate-to-severe active rheumatoid arthritis, after an insufficient response to anti-tumour necrosis factor (anti-TNF) agents. The authors concluded that abatacept as a second-line therapy was more effective and cost-effective than rituximab; and abatacept as a third therapy was more effective and cost-effective than a third anti-TNF. The methods and reporting were adequate, but the analysis and conclusions were weak.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
This study examined the cost-effectiveness of alternative sequences of biological treatments for patients with moderate-to-severe active rheumatoid arthritis, after an insufficient response to anti-tumour necrosis factor (anti-TNF) agents.

Interventions
Each sequence started with etanercept. The four following options were abatacept then adalimumab; rituximab then adalimumab; adalimumab then abatacept; or adalimumab then infliximab. Response was assessed at six months and patients remained on a drug if they successfully responded, otherwise they switched to the next drug in the sequence.

Location/setting
Italy/primary care.

Methods
Analytical approach:
Mathematical simulations synthesised the costs and benefits over two years. The authors stated that the study was conducted from the perspective of a public health care payer.

Effectiveness data:
The effectiveness data were from several clinical trials, including the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), the Research in Active Rheumatoid Arthritis (ReAct) trial, and the Randomized Evaluation of Long-term Efficacy of Rituximab (REFLEX) trial. Clinical effectiveness was estimated using low disease activity, which was defined as a disease activity score (DAS28) of 3.2 or less, or remission, defined as a DAS28 score of less than 2.6.

Monetary benefit and utility valuations:
Not relevant.

Measure of benefit:
The benefit measures were the number of days with low disease activity or remission over two years.

Cost data:
The direct medical costs included medical visits, laboratory tests, hospitalisations, imaging, physiotherapy, and adaptive aids. The costs of biological medications were based on their list price and recommended dosing in Italy. All other
resource items were estimated by a group of clinical experts. All costs were reported in Euros (EUR) for the price year 2008.

Analysis of uncertainty:
Uncertainty surrounding the model inputs was assessed using probabilistic methods (Monte Carlo simulation). The inputs were assigned lognormal distributions from their means and standard deviations.

Results
Over two years, the days with low disease activity were 102 for patients receiving abatacept then adalimumab after etanercept and the mean total cost was EUR 38,616. The days with low disease activity were 82 for those receiving rituximab then adalimumab, with a mean total cost of EUR 37,667. The days with low disease activity were 63 for those receiving adalimumab then abatacept, with a mean total cost of EUR 38,628. The days with low disease activity were 32 for those receiving adalimumab then infliximab, with a mean total cost of EUR 37,566.

For patients achieving remission, the mean days for abatacept then adalimumab were 52, with mean costs of EUR 38,583. The mean days for rituximab then adalimumab were 62, with mean costs of EUR 37,686. The mean days for adalimumab then abatacept were 21, with mean costs of EUR 38,522. The mean days for adalimumab then infliximab were nine, with mean costs of EUR 37,729.

The average cost per remission day and per low disease activity day were presented.

Authors’ conclusions
The authors concluded that etanercept then abatacept then adalimumab was more effective and cost-effective than etanercept then rituximab then adalimumab. After an insufficient response to two anti-TNF agents, abatacept was more effective and cost-effective than a third anti-TNF.

CRD commentary
Interventions:
The four treatment sequences were well described, and treatment success and the doses were from clinical trials. It was not clear whether other relevant treatment sequences existed.

Effectiveness/benefits:
A systematic review does not appear to have been conducted to identify the clinical trials to ensure that the best available evidence was used. Limited details of the selected trials were reported, making an assessment of their quality impossible, and the authors did not state how they calculated the relative clinical effects for each sequence. The comparability between the trials of the participants’ baseline socio-demographic and clinical characteristics, the withdrawal rates, and the patients’ previous treatments was not discussed; making any assessment of their validity difficult. The disease-specific benefit measures make comparisons across health conditions impossible, but the authors discussed the advantages of these measures.

Costs:
The cost categories were relevant to the stated perspective. For most cost categories, the sources for the unit costs and resources were not explicitly reported, but they appear to have been publicly available or provided by experts. For the biologic drugs, the sources of unit costs and doses were well reported. The costs were not reported by individual item. The price year was reported, which will allow reflation exercises for other time periods. Overall, the cost component of the analysis was not reported in detail.

Analysis and results:
The results were clearly reported. Average cost-effectiveness ratios were presented for each of the four sequences and the mean differences were analysed. An incremental analysis would have been informative for decision-makers, but was not undertaken. A probabilistic sensitivity analysis was satisfactorily conducted and the results were well presented in cost-effectiveness acceptability curves, but the usefulness of these curves, given the lack of an incremental analysis, is questionable. Discounting was not conducted; it was relevant for those costs and benefits incurred after one year, but given the two-year time horizon, this is likely to have had little impact.
Concluding remarks:
The methods and reporting were adequate, but the lack of an incremental analysis makes comparative conclusions on the cost-effectiveness of the alternative strategies weak.

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